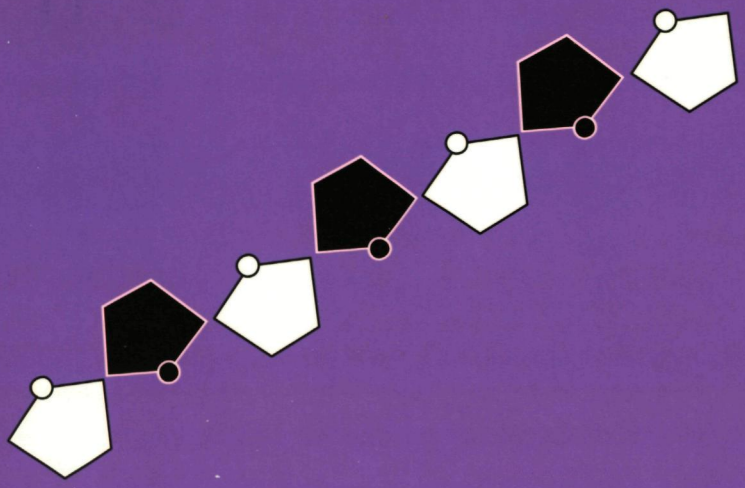
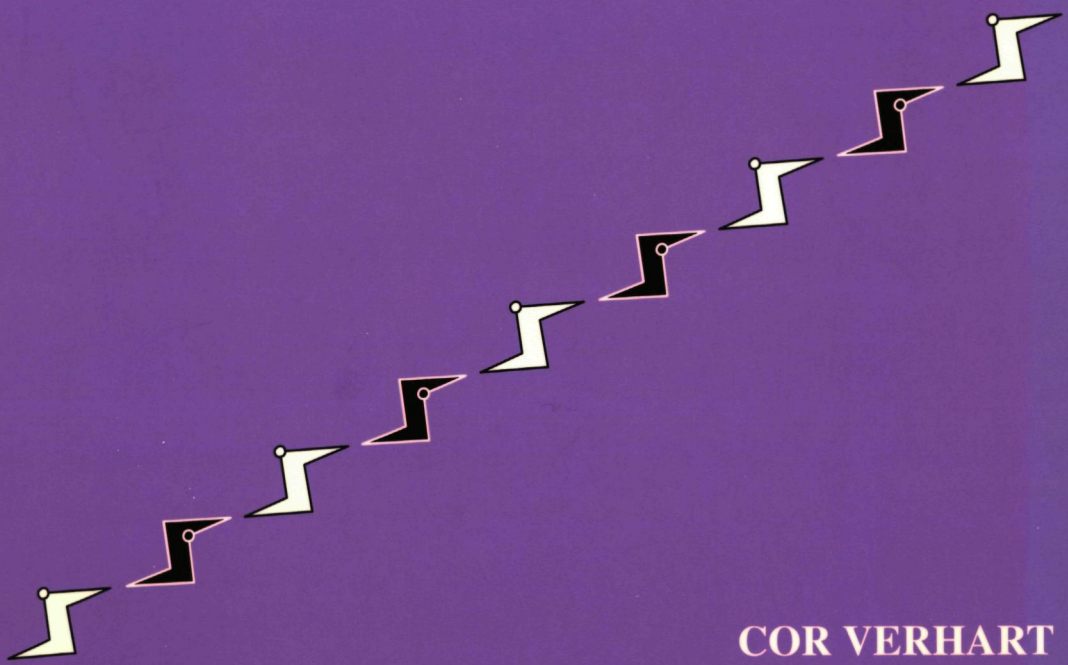


SOME APPROACHES TO THE INNOVATIVE CHEMICAL USE OF SUCROSE AND RELATED MONOSACCHARIDES



COR VERHART

SOME APPROACHES TO THE INNOVATIVE CHEMICAL USE OF SUCROSE AND RELATED MONOSACCHARIDES

Aan mijn ouders

Voor José

SOME APPROACHES TO THE INNOVATIVE CHEMICAL USE OF SUCROSE AND RELATED MONOSACCHARIDES

EEN WETENSCHAPPELIJKE PROEVE OP HET
GEBIED VAN DE NATUURWETENSCHAPPEN

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
AAN DE KATHOLIEKE UNIVERSITEIT NIJMEGEN,
VOLGENS BESLUIT VAN HET COLLEGE VAN DECANEN
IN HET OPENBAAR TE VERDEDIGEN OP
WOENSDAG 26 OKTOBER 1994
DES NAMIDDAGS TE 1.30 UUR PRECIES

DOOR

CORNELIS GERARDUS JOHANNES VERHART

GEBOREN OP 2 OKTOBER 1964
TE ELST

Promotor: **Prof. Dr. B. Zwanenburg**

Copromotor: **Dr. G.J.F. Chittenden**

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COR

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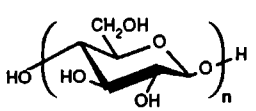
INTRODUCTION

1.1 Carbohydrates as chemical feedstocks

The carbohydrates comprise one of the major and most abundant classes of organic compounds occurring in nature. They constitute three quarters of the dry substance of plants, which is the main source of commercial carbohydrates, and are widely distributed in other life forms. They serve as a source of basic animal and human food, as the energy stores of cells, and as structural elements which gives them an important role in metabolic pathways. Plants contain polysaccharides, such as cellulose (**1**), hemicelluloses and pectins, which occur in their cell walls to provide structural solidity. Starch (**2**) (potato, maize, wheat), inulin (**3**) (chicory and jerusalem artichoke), and the disaccharide sucrose (**4**) (*saccharum officinarum*: cane sugar, *beta vulgaris*: beet sugar), act as energy sources. Hydrolysis of the polysaccharides **1-3** yields their constituent monosaccharides, D-glucose (**5**), D-fructose (**6**), and the disaccharides maltose (**7**) and cellobiose (**8**).



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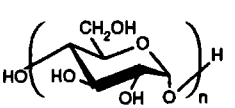

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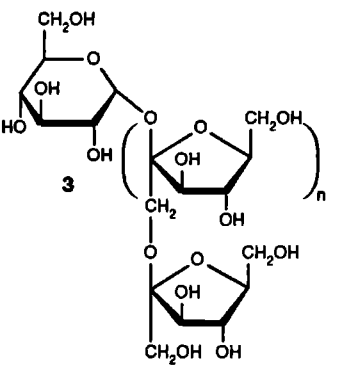

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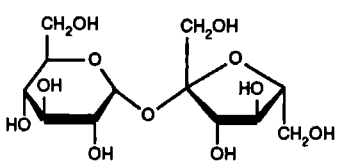

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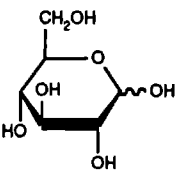

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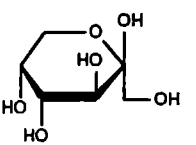

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Carbohydrates are a renewable feedstock since they are available annually from agricultural crops. They are inexpensive and possess high chemical and enantiomeric purity. Interest in the use of some carbohydrates as chemical raw materials has increased considerably during the last two decades due to the build-up of surplusses, especially within the European Community due to its common agricultural policy, and the long-term limitations on the use of non-regenerable fossil

feedstocks. In addition, the increasing demand for more environmentally friendly processes and products plays an important role in the interest of sugars as a competent and competitive source of raw materials. The dependency on fossil feedstocks as the main source of chemicals may be diminished by the development of products based on renewables (agrification). In order to be economically successful these products need to be produced at costs competitive with similar products based on petrochemicals.

The Netherlands, and the European Community as a whole, is facing agricultural surplusses in several product areas as already indicated. In 1985 the Dutch Ministeries of Economic Affairs and Agriculture and Fisheries decided to support a National Programme of Innovative Oriented Research on the development of the chemistry of carbohydrates (IOP-k). The large abundance of sucrose, the production in the Netherlands is estimated to be 10^6 tons per year, renders it a potentially attractive inexpensive starting material for organic synthesis.

The attractiveness of carbohydrates as potential raw materials can be explained by their relative cheapness, enantiomeric purity, and availability in bulk quantities in a variety of cyclic and acyclic forms, chain lengths, and oxidation states[1,2]. Most of the naturally occurring carbohydrates are inexpensive compared with other chiral materials and several, *e.g.* sucrose (**4**), D-glucose (**5**), D-fructose (**6**) and maltose (**7**), are in the price range of the commonly used organic solvents such as methanol and acetone[1]. Environmental restrictions are also of importance since most carbohydrates and their derivatives are non-toxic and are readily biodegradable. For the application in products for human consumption and personal care (*e.g.* food, cosmetics) this non-toxic character is essential. The enantiomeric purity of carbohydrates also makes them particularly useful for the development of synthetic chiral building blocks[2], and for use as chiral starting materials in the synthesis of enantiomerically pure compounds with important biological activities for the pharmaceutical and agrochemical industry. Most carbohydrates are neutral and hydrophilic and can be used as potential polar head-groups in non-ionic carbohydrate-based surfactants or amphiphiles[3].

In view of the easy accessibility of most carbohydrates in large quantities it is surprising that they are not utilized more generally on a much larger scale as raw marterials for the chemical industry. For convenient application inexpensive reagents and simple conversions into key intermediates are required. Many of the described routes, however, are of little practical value due to the large number of steps, use of expensive reagents, complex separation techniques, or difficulties in the developing of reliable scaling-up procedures[4]. Another reason for the limited utilization of more practical routes is that carbohydrates are obviously polyfunctionalized with hydroxyl groups of similar or identical reactivity, and that they have more chiral centres than required for non-sugar target molecules.

Sucrose (**4**) is chemically unsuitable for many synthetic transformations because of its multifunctionalization, which presents problems in selective reactivity or protection, and more importantly due to the sensitivity of the glycosidic bond to acid hydrolysis[5]. This tendency towards acid hydrolysis generally necessitates extremely mild reaction conditions. The constituent

monosaccharide units of sucrose, *i.e.* D-glucose (**5**) and D-fructose (**6**), are devoid of this deficiency and can be also used for the synthesis of useful intermediates and products. In this thesis, some studies aimed at alternative and practical methods for the preparation of useful products based on the innovative chemical use of sucrose and its constituent monosaccharides are described.

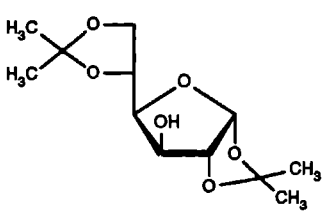
1.2 Aims and outline of the thesis

This thesis concerns the utilization of sucrose and related compounds as a source for basic and potentially useful products. The emphasis of the reasearch is on cheap innovative chemical conversions of sucrose and related compounds, with adaptibility to the larger scale industrial application of sucrose, rather than on the synthesis of speciality products. The use of sucrose as a practical bulk organic intermediate comprises a number of practical criteria:

- Products should be unique to sucrose or related compounds.
- Reactions should ideally be regioselective with limited use of simple protecting groups.
- Reagents should be simple and inexpensive.
- Short high yielding reaction sequences are preferred.
- The reaction(s) should have good scaling-up prospects and complex work-up procedures should be avoided.

It is known that selective esterification and other reactions are difficult to achieve with sucrose. In Chapter 2 the primary object was to extend and investigate further the direct selective esterification of sucrose, especially the sulphonylation, based on esterification with sterically hindered sulphonyl chlorides and by making use of partially acetylated sucrose derivatives. The synthesis of sucrose phosphates, and a modified synthesis of cyclic acetals of sucrose using a newly developed mild acetalation system is also described.

Chapter 3 deals with the isopropylidenation of sucrose, inulin and the related monosaccharides, employing a new mild acetalation method using catalytic amounts of iodine in acetone[6]. With sucrose efficient cleavage of the interglycosidic bond occurs, with concomitant isopropylidenation, to yield the di-*O*-isopropylidene acetals **9**, **10** and **11**. These acetals can also be obtained in a direct manner: **9** from D-glucose (**5**), and **10** and **11** from inulin (**3**) or D-fructose (**6**), using the same procedure.



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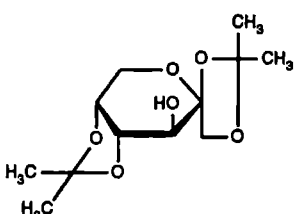

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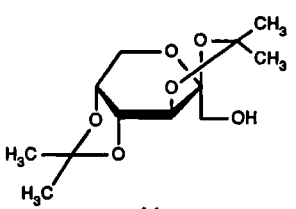

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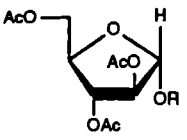
In Chapter 4 the iodine-catalyzed acetalation reaction was extended to include carbonyl reagents other than acetone. The synthesis of some benzylidene acetals is described, and the synthesis of the somewhat more unusual cyclohexylidene and cyclopentylidene acetals of D-glucose and D-fructose. Some examples of iodine-catalyzed transacetalation reactions are also described.

In Chapter 5 a novel method for the synthesis of a number of short and long-chain alkyl D-fructofuranosides (**12-13**) and D-glucofuranosides (**14-15**) is presented employing a new mild glycosidation method using various alcohols in the presence of catalytic amounts of iodine. The possible role of D-glucose dimethyl acetal in the glycosidation sequence using methanol was also investigated as a mechanistic model.



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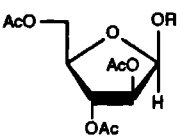
n = 1, 2, 3, 4, 8



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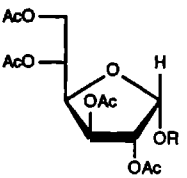
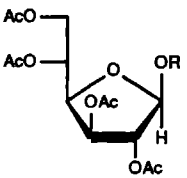


14 R = n-C_nH_{2n+1}, n = 1
16 R = n-C_nH_{2n+1}
n = 4, 8, 12



15 R = n-C_nH_{2n+1}, n = 1
17 R = n-C_nH_{2n+1}
n = 4, 8, 12

In Chapter 6 the iodine-catalyzed synthesis of some alkyl D-glucofuranosides (**16-17**) starting from the easily accessible 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**9**) is described.

Chapter 7 is devoted to the synthesis of long-chain alkylsulphonyl esters and ethers from the di-*O*-isopropylidene acetals **9**, **10**, and **11** of D-glucose and D-fructose. These could be of interest as surfactants.

Summaries in English and Dutch conclude this thesis.

1.3 References and notes

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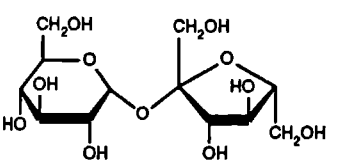
ESTERS AND ACETALS OF SUCROSE

2.1 Introduction

2.1.1 *Sucrose as bulk chemical for industrial application*

Sucrose (**1**), known commonly as table sugar, is by far the most widespread, and the most abundant, carbohydrate present in the sap of land plants. It is one of the most regenerable chiral natural products available in a state of unexcelled purity, in a highly crystalline form, on a very large scale, and at low cost. It has been produced as a food and sweetener since *ca* 2000 BC from the juice of sugar cane (*saccharum officinarum*), found in the tropics and semi-tropics, and since the early 1800's from sugar beet (*beta vulgaris*) in temperate climates. Sucrose, which is produced in far greater quantity, and in higher purity than almost any other organic material, is one of the leading world-commodities: its current annual production in all forms exceeds 100 million tons with a world market price of approximately 0.30 US $ per kg[1]. Sucrose is used almost exclusively by the food and other consumer good industries for sweetening purposes; chemical and non-food utilization is currently lower than 5%.

The potential value of **1** as a source of various industrial materials and intermediates had already been recognized in the early 1940's[2] and this led to the inception of the Sugar Research Foundation by the American industry in 1943, and subsequently through the International Sugar Research Foundation. The main goal was to develop new industrial non-food uses of sugar, *e.g.* by stimulating research into **1**, and to study the creation of new markets for the commodity.

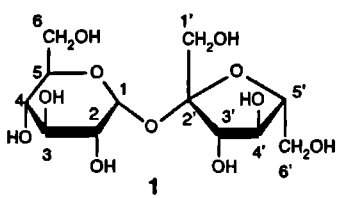


1

Interest in the use of **1**, and other carbohydrates, as industrial chemical feedstock has increased considerably during the last two decades because of the expected over-capacity in the agricultural industry (especially within the European Community), and the projected long-term limitations on the exploitation of non-regenerable fossil feedstocks. Additionally, environmental restrictions, in terms of bio-degradability and bio-compatibility on the use of a number of chemical products, also play an important role in the renewed interest of **1** as a potential source of industrial based materials.

Numerous and diverse uses for sucrose and its possible compounds have been proposed or patented, but, in practice, very few applications have been successfully developed. This was indicated earlier in a critical review[3] in 1970 of the initial 25 years of research carried out by the Sugar Research Foundation. Two reasons can be proposed for this observation. Firstly, for economic reasons the products have to be produced at costs competitive with similar products based on petrochemicals, and secondly sucrose is chemically a relatively intractable substance. Probably less than 100 well-defined derivatives of it have been described hitherto. Most of these have been produced under sophisticated conditions using time consuming protective group sequences, and extensive chromatographic separations, thereby making them unattractive commercially.

Relatively few products derived from sucrose have currently found commercial application. Some sucrose monoesters of long-chain fatty acids can be applied as detergents for domestic use, and for use as dispersing, stabilizing, and emulsifying agents in the pharmaceutical, food and agricultural industries. In several countries (*e.g.* Japan and France) sucrose esters are now permitted food additives. Sucralose (4,1',6'-trichloro-4,1'6'-trideoxy-*galacto*-sucrose **2**, Tate & Lyle), 650 times sweeter than sucrose, has been approved recently for application as a non-cariogenic sweetener by the Food and Drug Aministration (FDA) and is available as "Splenda" on the market in Canada as a food and beverage additive. The sucrose polyesters, *e.g.* Olestra^R (Proctor & Gamble), have been claimed as non-caloric fat substitutes, since these esters are not hydrolysed by lipases and pass through the intestine without alteration. Sucrose can be isomerised to isomaltulose[4] (Palatinose^R) in a process using the organism *Protaminobacter rubrum*. This product is as sweet as sucrose but non-cariogenic and has obvious future applications.



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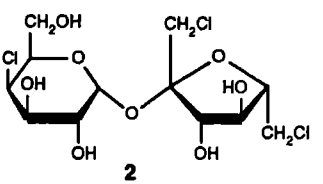

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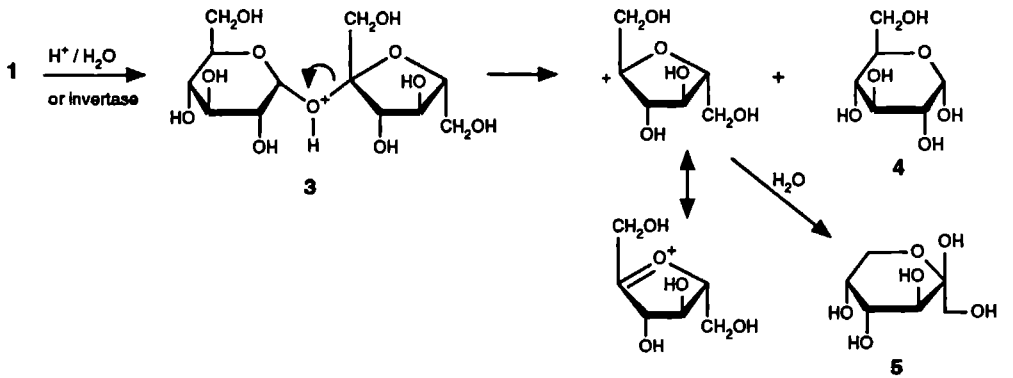
2.1.2 *Physical properties of sucrose*

Sucrose (**1**) is a non-reducing disaccharide in which the compositional sugars, D-glucose and D-fructose, are combined through the glycosidic hydroxyl groups of their anomeric centers (C-1 and C-2'). It can be named systematically as either β-D-fructofuranosyl α-D-glucopyranoside or α-D-glucopyranosyl β-D-fructofuranoside. In order to number the carbon atoms in the sucrose molecule systematically the carbons in the D-glucose moiety are designated with simple numerals, whereas those in the D-fructose moiety are given primed numerals.

The optically active disaccharide **1**, $[\alpha]_D$ +65.53^0 (H_2O), on hydrolysis with very dilute acid, cationic exchange resins, or by the enzyme *invertase*, yields equimolar proportions of D-glucose and D-fructose. The hydrolysate is *laevo*-rotary ($[\alpha]_D$ -28.2^0) and consequently the process became known as inversion, and the product as invert sugar. The glycosidic bond of sucrose is very sensitive to acid hydrolysis. The facile hydrolysis of **1** occurs by the collapse of a protonated oxonium ion **3**, to give D-glucose **4** and a D-fructofuranosyl carbocation, which then hydrates to give D-fructose **5** (Scheme 1).

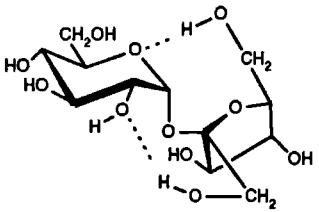
Scheme 1 *Hydrolysis of sucrose.*



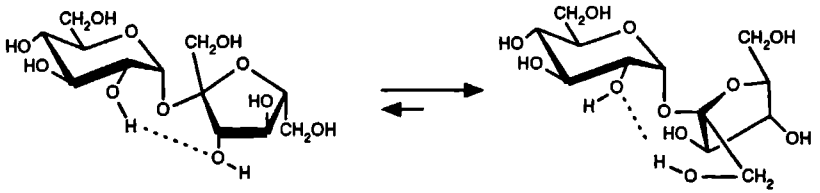
Structural aspects of sucrose, *i.e.* configuration and conformation, have been extensively studied by use of X-ray crystallography[5], neutron diffraction[6], ^{1}H-[7] and ^{13}C-NMR[8a-e] spectroscopy. All of the hydroxyl groups, excepting that at C-4, are hydrogen bonded with two important intramolecular bonds; 1'OH---O-2 and 6'OH---O-5 (Scheme 2). These bonds serve to "hold" the molecule in a well-ordered, rigid conformation in which the D-glucopyranosyl unit adopts a $^4C_1$ conformation while that adopted by the D-fructofuranosyl moiety is a $^4T_3$ twist. The conformation in aqueous solution, including the possible disruption of hydrogen bonding by solvation, has been the subject of much debate. Hard sphere exo-anomeric (HSEA) calculations together with ^{1}H and ^{13}C-NMR spectra of **1** (both in DMSO and D_2O), indicate that even in dilute solutions the 1'OH---O-2 hydrogen bond is still intact[7,9]. Application of isotope-shift measurements with SIMPLE (Secondary Isotope Multiplet Partially Labelled Entities) NMR spectroscopy of **1** in DMSO demonstrated the presence of two different conformations involving an extra intramolecular hydrogen bond, *i.e.* 3'OH---O-2, which is in competitive equilibrium with the 1'OH---O-2 hydrogen bond[10] (Scheme 2).

Scheme 2 *Conformation of sucrose in the crystal (A) and in solution (B).*

A) Crystal:



B) In solution:



Sucrose is very soluble in water, 2.07 g/g H_2O at 25^{0}C, and is also readily soluble in other protic solvents such as methanol and ethanol[11]. For most chemical reactions water is unsuitable, since it will inevitably participate, prevent, or interfere with the desired reaction pathway. The solubility of **1** in many non-aqueous solvents has been investigated[12]. Sucrose is insoluble in most organic solvents, so that reaction in solution requires the use of polar or hydrogen-bonding solvents (Table 1). Most commonly, pyridine, dimethyl sulfoxide, *N,N*-dimethylformamide, and *N*-methyl-2-pyrollidone are used for sucrochemical applications but their suspected toxicities renders them unacceptable for use in producing food and personal products. The solubility of **1** in a solution of lithium bromide in acetone is noteworthy and has been applied in the partial benzoylation of sucrose[13].

Table 1 *Solubility of sucrose in non-aqueous solvents[12].*

Solvent	Solubility (at 100^{0}C) g/100 g
dimethyl sulfoxide	58.7
morpholine	45.1
dipropyl sulfoxide	42
N-methyl-2-pyrrolidinone	33.5
N,N-dimethylformamide	29.6
2-methylpiperazine	29.5
propane-1,2-diol	11
pyridine	5.99
pyrazine	2.23
sulfolane	<1
dimethylsulfolane	<1
1,4-dioxane	<1

2.1.3 *Esterification of sucrose*

The fundamental chemistry of sucrose has been studied extensively and described in several reviews[3,14a-c]. The most widely studied and major area of interest is centred on selective esterification reactions of **1**. The multifunctionality of the sucrose molecule generally frustrates efforts to prepare single compounds of sucrose in high yields. The sucrose molecule possesses eight hydroxyl groups, three primary hydroxyl groups and five secondary hydroxyl groups. They are the only reactive functions available for derivatisation. The presence of the two types of hydroxyl groups in the sucrose molecule permits the potential synthesis of an enormous number of varied sucrose esters. In theory the direct esterification with just one type of group (*e.g.* an acetate) could give some 255 different compounds, which vary in the degree of substitution and the position of the ester group (Table 2).

Table 2 Numbers of isomers of O-derivatives of sucrose from mono- to octa-substituted.

Mono	8	Tri	56	Penta	56	Hepta	8
Di	28	Tetra	70	Hexa	28	Octa	1

Sucrose is a polyhydric alcohol which is in general difficult to esterify selectively. Several approaches have been used however, to achieve selective esterification of **1**, namely the use of protective functions or controlled direct esterification. The eight hydroxyl groups of sucrose exhibit subtle differences in their reactivities, and partial or selective esterifications can only be achieved under very carefully controlled reaction conditions. The methods for the selective protection of certain hydroxyl groups is of obvious advantage in the chemical manipulation of **1**. The most common routes to partially acylated sucrose derivatives have been *via* selectively protected intermediates, such as 6,1,6'-tri-*O*-trityl sucrose[15] and the cyclic acetal 2,1':4,6-di-*O*-isopropylidene sucrose (**10**)[16,17].

Generally, the primary hydroxyl groups at C-6 and C-6' are the most reactive, followed by the more hindered hydroxyl at C-1'. Of the five remaining secondary hydroxyls, the 2-OH and the 3'-OH would be anticipated to react more readily, because of their close proximity to the anomeric centres C-1 and C-2'[14a], and because the 2-OH is also involved in strong intramolecular hydrogen bonding. The order of acylation of the hydroxyl functions also depends on the nature of the acylating agent, since the substitution of one hydroxyl group may alter the relative reactivity of the remaining hydroxyl groups.

Sucrose is readily esterified to the corresponding octa-ester by reaction with an excess of the anhydride or chloride of a sterically unhindered organic acid in the presence of pyridine, or other suitable bases. Sucrose octaacetate is a well known bittering agent and denaturant prepared in this

way. However, careful treatment of **1** with 1.1 molar equivalents of acetic anhydride in pyridine at -40^{0}C gave, after chromatographic separation, 6-*O*-acetyl sucrose (40%)[18]. A detailed study[19] of the direct tri-benzoylation of **1** with benzoyl chloride in pyridine showed that the major product is the 6,1,6'-tri-*O*-benzoyl sucrose and led to the conclusion that the order of acylation is 6-OH > 1'-OH : 6'-OH > 2-OH : 3'-OH, the reactivity at 1' and 3' being greater than expected.

With sterically hindered sulphonyl chlorides, *e.g.* 2,4,6-trimethylbenzenesulphonyl chloride, reaction takes place almost exclusively at the primary hydroxyls of sucrose, even though normally the secondary 4-OH is more reactive than the primary 1'-OH on the fructose moiety[20]. The steric effects of the trimethylacetyl (pivaloyl) group is less marked as demonstrated by a study under a variety of conditions[21]. Reaction of **1** with pivaloyl chloride afforded a series of compounds, ranging from the di- to the hepta-pivalate, which were isolated and characterized. Trimolar pivaloylation of **1** afforded the 6,1,6'-tri-*O*-pivalate (42%) and the 6,6'-di-*O*-pivalate (22%) as the major products. Two principle, but divergent, reaction pathways have been suggested to exist between sucrose and its octapivalate in which the order of reactivity of the hydroxyl groups towards acylation are:

a) 6,6'-OH > 1'-OH > 4'-OH > 2-OH > 4-OH > 3'-OH > 3-OH;

b) 6,6'-OH > 1'-OH > 3'-OH > 3-OH > 4'-OH > 2-OH and 4-OH.

These results indicate that the numbers of isomers formed by substitution with only one type of group is, in practice, much smaller than the theoretically possible 255. However, selective mono-acylation of sucrose still remains a difficult task.

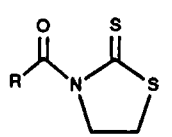
The sulphonate esters of sucrose have also been widely studied and are of considerable utility as synthetic intermediates for two main important aspects. Firstly, the esterification of sucrose with limited quantities of various sulphonyl halides shows greater selectivity, the general order of reactivity being 6-OH, 6'-OH > 1'-OH > 2-OH. Secondly, the resultant sulphonates then show significant differences in their preferences for substitution of the sulphonyloxy groups by nucleophiles. Their reactivity varies according to their position on the sucrose skeleton, with 6-OR > 6'-OR > 4-OR > 1'-OR in terms of the ease of their replacement. As discussed earlier *(vide supra)* a large number of isomers can arise in theory but the higher reactivity of the primary hydroxyls does simplify these reactions to some extent. Thus trimolar tosylation of **1** would be expected to yield the 6,1,6'-tritosylate, but chromatography revealed a mixture of products. Two different tritosylates namely, 6,1,6'- (26%) and 2,6,6'-tri-*O*-tosyl sucrose (7%), a crystalline 6,6'-di-*O*-tosylate, and a small amount of 2,6,1',6'-tetra-*O*-tosyl sucrose were also isolated and identified[22]. Tetramolar tosylation of **1** afforded 6,1',6'-tri-*O*-tosyl sucrose (40%) and 2,6,1',6'-tetra-*O*-tosyl sucrose (32%)[23]. The hindered 1'-OH is, therefore, less reactive than the other primary 6- and 6'-OH groups, and the order of reactivity of sucrose to tosyl chloride is 6-OH, 6'-OH > 1'-OH > 2-OH > other OH groups.

Greater selectivity in the synthesis of the primary sulphonate esters of sucrose has been achieved by using the bulkier 2,4,6-trimethylbenzene (trimsyl)[20] or 2,4,6-triisopropylbenzene (tripsyl)[24] sulphonyl chloride. These reagents lead to direct isolable crystalline derivatives in good

yields without resorting to chromatography, but the reagents are relatively expensive.

An important alternative route to sucrose esters is by transesterifications reactions whereby an acyl group is transferred from a simple ester to sucrose under basic conditions. Snell and Osipow[25,26] developed a process for the preparation of sucrose monoesters; **1** in DMF solution was heated with the methyl ester of a fatty acid and using K_2CO_3 as a catalyst to form prepoderantly sucrose monoesters (mainly the 6- and 6'-isomers), with liberation of methanol. Further development[27] of this reaction led to a preparative method for the synthesis of sucrose monoesters with reproducible and essentially quantitative yields and products that contained about 20% of di- and 80% of monoesters. Another important reaction for the synthesis of sucrose monoesters is the Mitsunobo reaction[28]. The preparation of 6-*O*-palmitoyl sucrose (47%) was described[29] by treatment of **1** with palmitic acid (1.2 equivs), triphenyl phosphine (1.4 equivs) and di-isopropyl azodicarboxylate (1.4 equivs) in DMF at room temperature for 76 h. The selectivity of this reaction is explained in terms of steric hindrance of the appropriate intermediates, in such a way that the least hindered 6-OH is transformed into the desired monoester.

A two step chemo-enzymatic synthesis of 6'-*O*-acylsucroses has been described[30]. This was recently extended to the selective synthesis of 2-*O*-acylsucroses[31], without using an enzymatic step. Acylation of **1** in anhydrous pyridine with 3-acyl-thiazolidine-2-thione **6** in the presence of a catalytic amount of sodium hydride resulted in the formation of the 2-*O*-acyl sucrose as the major product (45-70%) together with small amounts (3-10%) of the 3-*O*-acyl sucrose. Application of the reaction in DMF, a more convenient solvent for sucrose, with weakly nucleophilic bases was also investigated. The use of 1,8-bis(dimethylamino)naphthalene (proton sponge) gave lower overall yields and lower regioselectivity, 3-*O*-acylsucroses being obtained in larger amounts. With triethylamine or 1,4-diazabicyclo[2.2.2]octane (DABCO) as base acylation occurred readily and 2-*O*-acylsucroses were isolated in 41-46% yield. These results are comparable to the acylation with 3-acyl-5-methyl-1,3,4-thiadiazole-2(*3H*)-thiones **7** using DABCO as the base at lower temperatures which occurs selectively at the 6'-OH of the fructose moiety[30]. The selectivity of this reaction was explained by assuming that the 2-OH, which serves as an hydrogen bonding acceptor even in aprotic solvents (section 2.1.2), will be the most acidic hydroxyl group. Activation with a catalytic amount of sodium hydride will lead to a highly nucleophilic 2-oxyanion which reacts with the esterifying agent to give the 2-*O*-acyl derivative selectively.



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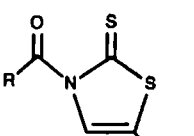
R = $(CH_2)_6$-CH_3
R = $(CH_2)_{10}$-CH_3
R = $(CH_2)_{16}$-CH_3
R = $(CH_2)_2$-C_6H_5



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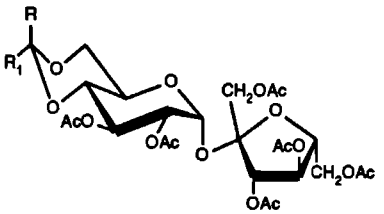
Enzyme-mediated reactions could be of promise in the synthesis of specific sucrose esters. In most chemical acylations the 6-OH and 6'-OH funtions are usually the most reactive. Synthesis of 1'-*O*-esters is difficult because of the low reactivity of the 1'-OH group. Surprisingly, Riva *et al*[32] noted the regioselective esterification of **1** with a protease (*B subtilicin*), using trichloroethyl butyrate in a solution of DMF, to give sucrose 1'-*O*-butyrate. Further investigation[33] of this protease-catalyzed trans-esterification revealed, however, that the scope of the reaction was limited to the introduction of short-chain acyl groups. The efficiency of the conversion, and the isolated yields of sucrose monoesters, dropped dramatically as the length of the acyl chain increased.

Novel approaches towards influencing the selectivity of certain hydroxyl groups have utilized organometallic and inorganic reagents to enhance the nucleophilicity of the hydroxyl groups towards acylation. This can be achieved by the use of transition metal chelates[34]. It is presumed that complexation of the "hard" ligating groups of a carbohydrate moiety with a "soft" metal cation will enhance the nucleophilicity of those groups involved and hence influence their selectivity towards acylating agents. A 98% yield of monoesters based on GLC and mass spectroscopy was claimed when **1** in DMF was treated with a mixture of sodium hydride, $CoCl_2$, and acetic anhydride (2:1:1.2). The products were not, however, isolated or characterized. The major products from analogous reactions in pyridine for both acetylation and butyroylation have been isolated in 60% yield, and identified by NMR as the 3'-*O*-esters[14a].

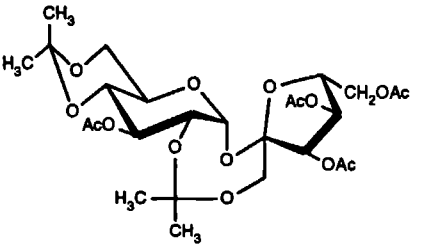
2.1.4 *Acetals of sucrose*

Carbohydrates, like other aliphatic diols, can react with aldehydes or ketones to form cyclic acetals or ketals. Acetalation reactions are widely used in carbohydrate chemistry for the synthesis of useful intermediates whereby the hydroxyl functions are protected at specific positions. Despite their obvious importance as synthetic intermediates, cyclic acetals of sucrose long defied preparation due to the acid lability of **1** (section 2.1.2) using conventional acetalation procedures, which gave rise to the formation of individual acetals of D-glucose and D-fructose. Previously, it had been considered that steric factors precluded the formation of the simple cyclic acetals of sucrose.

The first synthesis of a characterized cyclic acetal derivative of sucrose was reported in 1974 by Khan[35]. The acid-lability problem was circumvented by utilising α,α-dibromotoluene in pyridine at elevated temperature (85^{0}C) and, after acetylation, 4,6-*O*-benzylidenesucrose hexa-acetate **8** (35%) was obtained. Subsequently, the acetonation of **1** with 2,2-dimethoxypropane (DMP) in DMF in the presence of *p*-toluenesulphonic acid as catalyst, gave the 4,6-*O*-isopropylidene (**9**) and the 2,1':4,6-di-*O*-isopropylidene (**10**) derivatives in good yields[16]. The unique eight-membered cyclic 2,1'-*O*-isopropylidene acetal of **10** bridges the two constituent rings in sucrose and is more stable towards acid hydrolysis than is the 4,6-*O*-acetal group[36]. The replacement of DMP by either cyclohexylidene or benzaldehyde dimethyl acetals gave only the corresponding 4,6-*O*-cyclic acetals[37] of sucrose.



8 R = H, R_1 = Ph
9 R = R_1 = CH_3



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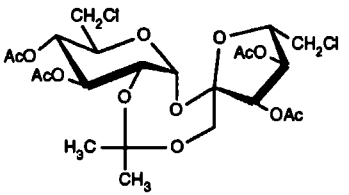

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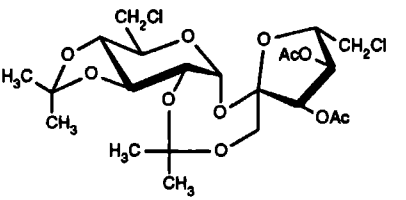
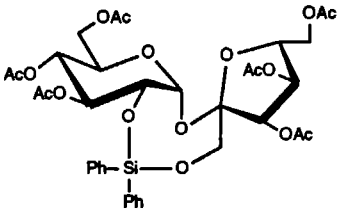


12

In order to study the formation of acetals at other positions in the sucrose molecule, usage of the 2,2-dimethoxypropane-induced acetalation reaction with 6,6-dichloro-6,6'-dideoxysucrose gave the corresponding 2,1'-*O*-isopropylidene acetal **11** (37%), together with the 2,1':3,4-di-*O*-isopropylidene derivative **12** (40%). Protection of all three primary hydroxyl groups with trityl groups directed the course of the reactions with the DMP reagent to the 2,3-*O*-isopropylidene (24%) and 3,4-*O*-isopropylidene (20%) derivatives[38]. In general the ease of formation of isopropylidene acetals of sucrose proceeds in the order of 4,6 > 2,1' > 2,3 > 3,4.

High yields of kinetic acetal products have also been achieved by the use of 2-methoxypropene. Treatment of **1** with 2-methoxypropene (5 equivs) in dry DMF in the presence of strictly limited amounts of *p*-toluenesulphonic acid at 70^0 (40 min) was reported to give, after acetylation, the diacetal **10** in 70% yield[39]. The 4,6-*O*-acetal **9** was obtained in 60% yield when the reaction was performed with 1.5 molar excess of the reagent. The synthesis of phenylsilylene acetals of sucrose has also been reported[40] using dimethoxyphenylsilane in DMF with catalytic amounts of *p*-toluenesulphonic acid. Treatment of **1** with this reagent afforded, after acetylation, the expected eight-membered 2,1'-*O*-silylene acetal **13** (46%) and the unique 2,1'-6,6'-di-*O*-(diphenylsilylene) acetal **14** (4%), which contains a twelve-membered acetal ring. The expected 4,6-*O*-silylene acetal was not formed because this derivative would introduce an unfavorable axial phenyl group onto the six-membered chair conformation.



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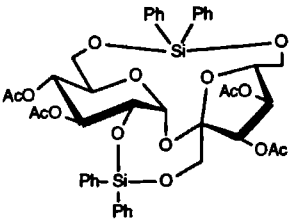

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2.1.5 *Aim of the research*

The primary objective of the research described in this chapter was to extend and investigate further the direct esterification of sucrose, particularly the sulphonylation. In section 2.2, sulphonate esters of sucrose were synthesized by direct esterification of sucrose using the sterically hindered D-(+)-10-camphorsulphonyl chloride. An alternative approach is also presented making use of partially acetylated sucrose derivatives for the synthesis of sucrose sulphonate esters.

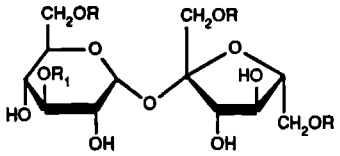
Section 2.3 deals with the synthesis of sucrose phosphates, a different class of sucrose esters, by the direct reaction of sucrose with diphenyl phosphorochloridate.

Finally, section 2.4 is devoted to the modified synthesis of cyclic acetals of sucrose as potentially useful intermediates using a new developed mild acetalation system of 2,2-dimethoxypropane in the presence of catalytic amounts of *p*-toluenesulphonic acid in pyridine.

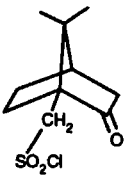
2.2 Sulphonate esters of sucrose

The selective esterification of sucrose is difficult to achieve (section 2.1.3) and often results in the formation of differently substituted sucrose esters and positional isomers thereof, due to the low chemical selectivity of the eight available hydroxyl groups. For some practical purposes however, mixtures of these can be used as such. The synthesis of the interesting sucrose sulphates by reaction of chlorosulphonic acid has also been reported[3], but none of these products have so far been investigated. Sucrose sulphonates are interesting compounds since selective S_N2 displacement reactions are possible with a variety of nucleophiles. The sulphonate esters of sucrose can also be esterified with fatty acids which could result in bio-degradable surfactants and emulsifying agents.

Esterification of sugars by reaction with sulphonyl halides in pyridine is the most common sulphonylation procedure employed in carbohydrate chemistry, especially for *p*-toluenesulphonylation (tosylation). The tetratosylation of **1** with tosyl chloride in pyridine gives 2,6,1',6'-tetra-*O*-tosyl sucrose **15** (30%) as the major product[23]. Tripsyl chloride (2,4,6-triisopropylbenzenesulphonyl chloride) is much more selective in its reaction with the primary hydroxyl groups of sucrose and affords the 6,1'6'-tri-*O*-tripsyl sucrose **16** as the main product[24], but it is also a relatively costly reagent.



15 R = R_1 = Ts
16 R = Trp, R_1 = H



17

Synthesis of camphorsulphonate esters

In order to investigate cheaper reagents that may also provide greater selectivity, the use of D-(+)-10-camphorsulphonyl chloride (**17**) was considered for the direct esterification of **1** in pyridine. It was thought that the greater bulk of the camphor skeleton may induce more selective substitution of the sucrose molecule. The sulphonyl chloride **17** is readily available from inexpensive D-(+)-10-camphorsulphonic acid by treatment with thionyl chloride in the presence of a catalytic amount of DMF[41]. Sucrose (**1**) was treated with varying amounts of **17** in dry pyridine at 0°C in attempts to achieve greater selective sulphonylation.

Table 3 The reaction of 1 with sulphonyl chlorides.

$$C_{12}H_{22}O_{11} \xrightarrow[pyr,\ 0^0C]{R\text{-}Cl} C_{12}H_{22-n}O_{11}(R)_n$$

Acylating agent[a]	Time	Products	D.S.[b] (n)	Yield[c]
4 equiv Ts-Cl	72 h	**15** Ref. 23		30%
5 equiv Trp-Cl	18 h	**16** Ref. 24		50%
4 equiv Cs-Cl	18 h	$C_{12}H_{22-n}O_{11}(Cs)_n$	4 3	13% 2%
3 equiv Cs-Cl	18 h	$C_{12}H_{22-n}O_{11}(Cs)_n$	4 3	5% 13%
3.5 equiv Ds-Cl	16 h	$C_{12}H_{22-8}O_{11}(Ds)_n(Ac)_{8-n}$	2 1	18% 24%

a) Ts-Cl. Tosyl chloride; Trp-Cl: Tripsyl chloride, Cs-Cl Camphorsulphonyl chloride **17**; Ds-Cl: 1-Decanesulphonyl chloride **18**.
b) average degree of substitution, determined by calculation from the elemental analysis or ^{1}H-NMR spectrum of the product.
c) after column chromatography.

From the results obtained (Table 3) selective esterification of **1** was not achieved using this approach. TLC-analysis of the reactions indicated complex product mixtures containing a wide range of differently substituted camphorsulphonyl esters of **1**, and positional isomers thereof, and only the

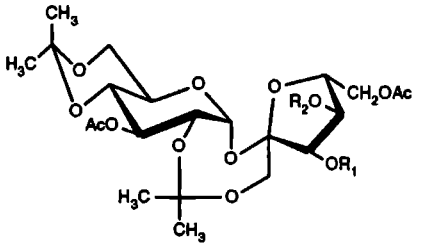
average degree of substitution (D.S.) could therefore be determined. The main products, however, seemed to be derivatives with an average D.S. of three to four camphorsulphonyl groups, which could be isolated by flash column chromatography. These were stable crystalline products but isolable in only moderate yields. By analogy with the tosylation and tripsylation, the products isolated containing three camphorsulphonic substituents were probably the 6,1',6'-positional isomer. Benzoylation of the isolated products afforded some corresponding stable compounds but these did not unfortunately provide sufficient further structural information.

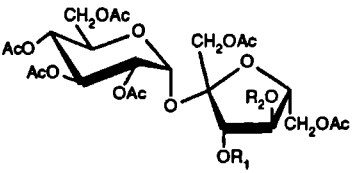
The reaction of **1** with the chloride **17** seems to be more complex than expected. The use of this reagent did not result in a more selective substitution of sucrose. This could be due to the fact that the sulphonyl group of **17** is not attached directly to the camphor skeleton but to an exocyclic carbon, reducing its effective steric bulk.

For comparative purposes the sulphonylation of **1** was also investigated with a different type of reagent, namely with the long chain alkyl derivative 1-decanesulphonyl chloride (**18**). Although less selectivity was expected this sulphonylation reaction led to the formation of mono- and di-substituted alkylsulphonyl-*O*-sucroses which could be isolated as their corresponding acetates. The overall reaction rate was apparently much slower than with camphorsulphonyl chloride since the formation of higher esters was not detected (TLC).

Sulphonate esters from partially acetylated sucrose derivatives

The acetals of sucrose *(vide supra)* could also provide another route to the specific formation of sulphonate esters of **1**. Selective de-*O*-acetylation of 2,1:4,6-di-*O*-isopropylidenesucrose tetra-acetate (**10**) using methanolic ammonia at low temperatures has been examined by Khan *et al*[42]. At -10^{0}C (15 min), the reaction afforded an inseparable mixture of the 3'- (**19**) and 4'-monohydroxy (**20**) compounds (32%) and the 3',4'-dihydroxy compound (**21**) (30%) together with starting compound (**10**) (24%). When the reaction was repeated at -10^{0}C (0.5 h), followed by 3.5 h at 5^{0}C, the 3',4'-dihydroxy compound **21** could be isolated in 35% yield. From the results it was deduced[42] that the order of hydrolysis of the four acetyl groups on the acetal **10** is: O-3' ≈ O-4' > O-6' > O-3. It is significant that de-esterification is preponderant on the fructofuranoside ring. Selective tosylation of the 3,6-diacetate **21**, followed by column chromatography led to the isolation of the 3',4'-ditosylate **22**, the 4'-tosylate **23** and the 3'-tosylate **24** in yields of 4, 3 and 31%, respectively. From these products the corresponding peracetylated derivatives **29**, **30** and **31** were obtained by deacetalation using aqueous acetic acid, followed by conventional acetylation[42]. These results indicated that the hydroxyl group on C-3' is more reactive towards tosylation than that on C-4', the general order of reactivity for tosylation of the hydroxyl groups on the fructoside ring being 6'-OH > 1'-OH > 3'-OH > 4'-OH[42].





10 $R_1 = R_2 = Ac$
19 $R_1 = H, R_2 = Ac$
20 $R_2 = H, R_1 = Ac$
21 $R_1 = R_2 = H$
22 $R_1 = R_2 = Ts$
23 $R_1 = H, R_2 = Ts$
24 $R_2 = H, R_1 = Ts$

25 $R_1 = R_2 = Ac$
26 $R_1 = H, R_2 = Ac$
27 $R_2 = H, R_1 = Ac$
28 $R_1 = R_2 = H$
29 $R_1 = R_2 = Ts$
30 $R_1 = Ac, R_2 = Ts$
31 $R_2 = Ac, R_1 = Ts$

An alternative route to partially acetylated derivatives of sucrose, as starting compounds for the synthesis of sucrose sulphonate esters, is the selective deacetylation of the octa-acetate of sucrose (**25**). This has been achieved by chromatography using a column of alumina with chloroform as the eluent. This afforded hepta-*O*-acetylsucroses in which the C-6' (9%), C-4 (3%) and C-4' (6%) hydroxyl group were unsubstituted[43]. More recently, Capek *et al*[44] have reported the isolation of hexa-*O*-acetylsucrose by an adaptation of this method using potassium carbonate incorporated into the alumina, with methanol being used as the eluent. Material corresponding to hexa-*O*-acetylsucrose was isolated (34%) and its subsequent reaction with *p*-toluenesulphonyl chloride in pyridine provided the crystalline 3',4'-di-*O*-tosylsucrose hexa-acetate (**29**) which was identical with the di-tosylate derivative prepared earlier[42] from the di-*O*-isopropylidene acetal **10**. From these results and the analysis of the hexa-*O*-acetylsucrose it was concluded that the deacetylation of sucrose octa-acetate is again highly regioselective for those ester groups on the fructofuranoside ring.

An alternative approach which was investigated in the current study also made use of partially deacetylated sucrose derivatives derived from the octa-acetate (**25**). These were subjected to *p*-toluenesulphonylation reactions to give the corresponding tosylates. The partially deacetylated sucrose derivatives were prepared by using a new reagent combination, namely iodine in methanol. The course of deacetylation was followed by thin-layer chromatography, from which the degree of acetylation could be assessed.

The deacetylation reaction of **25** with catalytic amounts of iodine (0.025 equiv) in methanol could be performed at room temperature, however the procedure proved to be more efficient when the mixtures were heated under reflux. The main products which could be isolated from the reaction mixture after column chromatography were shown to be hepta-*O*-acetylsucrose (13%) and a hexa-*O*-acetylsucrose (21%).

The ^{1}H-NMR spectrum of the isolated hepta-acetate was, to a great extent, similar to that of the octa-acetate **25** except for the resonances of H-3' and for H-4'. This suggested that the hepta-*O*-acetylsucrose consisted mainly of compounds **26** and **27** with the C-3' and C-4' hydroxyl group, respectively, being free. In order to confirm the structure of the hepta-acetate derivative it was subjected to *p*-toluenesulphonylation and it afforded the corresponding tosylate (68%). The ^{1}H-NMR spectrum of the tosyl-*O*-sucrose hepta-acetate was very similar to that of the 3'-tosylate **31**[42], indicating that the tosyl group was most likely at the C-3' position. The mass spectrum of the material also indicated the presence of the tosyl group in the fructofuranosyl cation (ion at *m/e* 443).

TLC-analysis of the isolated hexa-acetate suggested a two-component mixture in which one compound preponderated. Signals assigned to H-1, H-2, H-3 and H-4 in the ^{1}H-NMR spectrum between 4.8 and 5.8 ppm of the major compound were identified on the basis of their multiplicities and coupling constants. In comparison with the spectrum of **25** the signals of H-3' and H-4' seemed to be absent in this region, which indicated that the major compound is most probably the hexa-acetate **28** with the C-3' and C-4' hydroxyl groups being unsubstituted. Treatment of the hexa-acetate with *p*-toluenesulphonyl chloride gave the corresponding di-tosylate derivative (83%). The ^{1}H-NMR spectrum of the di-tosyl-*O*-sucrose hexa-acetate exhibited, similar to that of **29**[42], two methyl peaks at 2.46 and 2.45 ppm. The rest of the spectrum was also similar to that of the octa-acetate (**25**), except for a small, relative upfield shift of ~0.2 ppm for the signals of H-3' and H-4', indicating that the two tosyl groups were most probably located at the C-3' and C-4' position. The proposed structure of the di-tosyl-*O*-sucrose hexa-acetate was also supported by its mass spectrum, which contained peaks for ions due to the glucopyranosyl (*m/e* 331) and to the fructofuranosyl (*m/e* 555) cations, respectively, which indicated the presence of the two tosyl groups in the fructofuranosyl moiety.

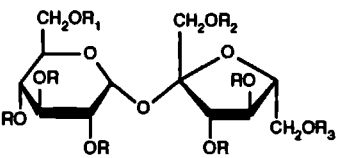
From the results obtained it can be concluded that the iodine-mediated deacetylation of sucrose octa-acetate is a suitable alternative method for the preparation of some selective deacetylated derivatives of sucrose. It is possible to use these derivatives for the synthesis of some sulphonate esters from sucrose.

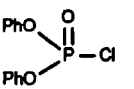
In the current study the partially deacetylated sucrose derivatives were prepared by using very low catalytic amounts of iodine in methanol (0.04% w/v). This results is in contradiction with an earlier study[45]. It had been demonstrated in that study that various carbohydrate acetals can be cleaved by dilute solutions (0.5-1%) of iodine in methanol to give mainly product mixtures of glycofuranosides. Benzylidene and isopropylidene acetals can be cleaved at room temperature or by heating under reflux for short periods. It was claimed[45] that under the applied conditions acetate groups were stable and not cleaved despite the fact that the iodine concentrations were much higher than those used here. The current study shows that under the applied conditions of using strictly limited iodine concentrations acetate functions can be cleaved and that the method can be used to prepare partial acetylated sucrose dertivatives.

During the current studies of iodine-mediated deacetylation it was also noted that iodine could be used as catalyst in the reverse reaction, namely the synthesis of acetates of **1**. Treatment of sucrose in acetic anhydride in the presence of catalytic amounts of iodine (0.1 equiv) at room temperature afforded the octa-acetate (**25**, 53%). The result indicated that **25** was formed without any significant breakdown of the glycosidic linkage.

2.3 Phosphorylation of sucrose with diphenyl phosphorochloridate

The phosphates of sucrose constitute a different class of interesting sucrose esters. Few phosphates of sucrose have been described hitherto, and those that have, *e.g.* 6'-*O*-phosphate sucrose (**34**)[48] which is an intermediate in the biosynthesis of sucrose, have required extensive blocking group regimes for their synthesis. Higher substituted phosphates of sucrose could be of biological interest, and possibly as basic intermediates for the design of new surfactants.





32

33 $R = R_2 = R_3 = H$, $R_1 = PO(OH)_2$
34 $R = R_1 = R_2 = H$, $R_3 = PO(OH)_2$
35 $R = R_1 = R_3 = H$, $R_2 = PO(OH)_2$
36 $R = R_2 = R_3 = H$, $R_1 = PO(OPh)_2$
37 $R = R_1 = R_2 = H$, $R_3 = PO(OPh)_2$

38 $R = R_1 = R_3 = H$, $R_2 = PO(OPh)_2$
39 $R = R_2 = R_3 = Ac$, $R_1 = PO(OPh)_2$
40 $R = R_1 = R_2 = Ac$, $R_3 = PO(OPh)_2$
41 $R = R_1 = R_3 = Ac$, $R_2 = PO(OPh)_2$

Diphenyl phosphorochloridate (**32**) is commonly used in both peptide[49] and carbohydrate chemistry[50,51] as a protective group or as a phosphorylating agent. It has been used *inter alia* for the preparation of mixed anhydrides for peptide coupling[49] and in the synthesis of several sugar phosphates such as D-glucose 6-phosphate[52] and D-arabinose 1,5-diphosphate[50]. It is relatively stable and gives diphenyl phosphate esters on reaction with suitable hydroxyl groups[52]. In most cases the reagent is used for the stereoselective introduction of the phosphate functionality at the desired position after selective manipulation with protecting groups of the appropriate substrate. The phenyl groups can be removed subsequently, usually by platinum oxide catalyzed hydrogenation[53], to give the free phosphate mono-ester.

In general, when two or more unsubstituted hydroxyl groups are available for esterification, a primary hydroxyl group can be phosphorylated preferentially using restricted amounts of **32**. In these reactions it is known[54] that when two suitably disposed contiguous secondary hydroxyl groups react with **32**, initial monophosphorylated products may undergo attack at phosphorus by the remaining hydroxyl group with elimination of phenol to give a cyclic tri-ester. Considering the *trans*-equatorial disposition of the hydroxyl groups in the glucose part and the all-*trans* configuration in the fructose moiety of sucrose makes cyclic phosphate formation less likely as an alternative pathway in the

reaction of sucrose with diphenyl phosphorochloridate. It was thought likely that **32** could provide selective reactions with the primary hydroxyl groups of sucrose. There are no reports heretofore of the direct and possible selective reaction of **1** with this reagent. In this study sucrose was treated with varying amounts of **32** in dry pyridine at 0^0C in attempts to achieve selective phosphorylation.

Table 4 The reaction of 1 with diphenyl phosphorochloridate.

$$C_{12}H_{22}O_{11} \xrightarrow[pyr\ ,\ 0^0C]{DPP\text{-}Cl} C_{12}H_{22-n}O_{11}(DPP)_n$$

DPP-Cl [a]	Time	Products	D.S.[b] (n)	Yield[c]
4 equiv	17 h	$C_{12}H_{22-n}O_{11}(DPP)_n$	5 4 3	4% 18% 11%
3 equiv	17 h	$C_{12}H_{22-n}O_{11}(DPP)_n$	3 2	29% 16%
1 equiv	17 h	$C_{12}H_{22-n}O_{11}(DPP)_n$	1	28%
1 equiv	60 h	$C_{12}H_{14}O_{11}(DPP)_1(Ac)_7$	1	31%

a) DPP-Cl: Diphenyl phosphorochloridate **32**. b) average degree of substitution, determined by calculation from the elemental analysis or ^{1}H-NMR spectrum of the product. c) after column chromatography.

From the results obtained (Table 4) it was concluded that selective phosphorylaton to give tri-substituted sucrose derivatives was not achieved using this approach. The products were mixtures of differently substituted diphenylphosphate esters of **1**, and positional isomers thereof (TLC), and only the average degree of substitution could therefore be determined. The main products which could be isolated by column chromatography as stable compounds seemed to be the tri- and di-substituted diphenylphosphoryl derivatives of **1**. These should be, most logically, the 6,6',1' and 6,6' positional isomers, respectively.

More selectivity was apparently achieved in the mono-phosphorylation of sucrose. Treatment of solution of sucrose in pyridine with one equivalent of **32** afforded a mono-substituted diphenylphosphoryl-*O*-sucrose which could be isolated by column chromatography in reasonable to moderate yields. Replacement of the chromatographic purification step by a standard extraction with 1-butanol afforded the product in approximately the same yield. The ^{31}P-NMR spectrum of the mono-phosphorylated derivative of **1** exhibited three different signals at approximately -14 ppm, indicating the possible presence of three different mono-substituted diphenylphosphorylated sucroses, *i.e.* **36**, **37**, and **38**, phosphorylated at the C-6, C-6' and C-1' position, respectively. Treatment of the diphenylphosphoryl-*O*-sucrose under standard conditions of acetylation afforded the corresponding peracetate. The ^{1}H-NMR spectrum of the diphenylphosphoryl-*O*-sucrose hepta-acetate clearly exhibited signals arising from H-1, H-2, H-3 and H-4, and was very similar to

that of sucrose octa-acetate (**25**). A more detailed analysis of the region 5.7-4.7 ppm revealed the presence of three similar signals for each individual hydrogen atom (H-1 to H-4) of the mono-substituted isomers which could be assigned definitively. This slight differences in appearance of the chemical shifts of the hydrogen atoms of the three isomers is most probably due to the large shielding effect of the two phenyl groups attached to the substituent at the primary 6-, 6'- or 1'-position, respectively. The integration of the three doublet signals for H-1 at 5.6 ppm and three double doublet signals for H-2 at 4.8 ppm showed a distribution of 48, 41 and 11%, which is similar to the distribution of the signals in the ^{31}P-NMR spectrum of the non-acetylated product. This indicated that the three mono-substituted compounds are most probably the 6-diphenylphosphoryl (**39**), 6'-diphenylphosphoryl (**40**) and 1'-diphenylphosphoryl (**41**) acetates, respectively. The proton decoupled ^{31}P-NMR spectrum of the acetylated phoshate ester product, presumably a mixture of **39**, **40** and **41**, again revealed the presence of three different resonances at approximately -14 ppm, which appeared as triplet signals in the non-decoupled spectrum (Figure 1).

Figure 1 The ^{31}P-NMR spectrum (δ -15.1 - -13.1 ppm) of the mono-substituted sucroses **39**, **40** and **41**.

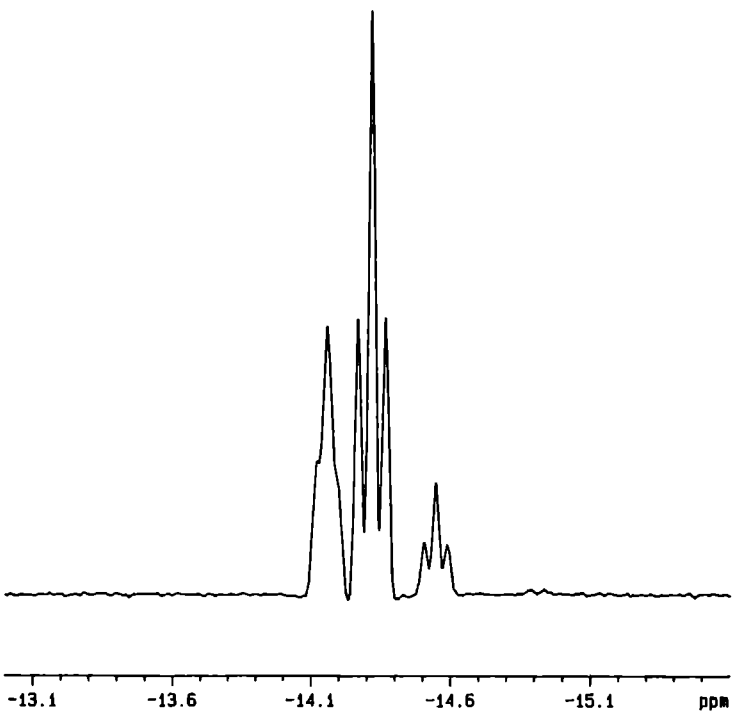
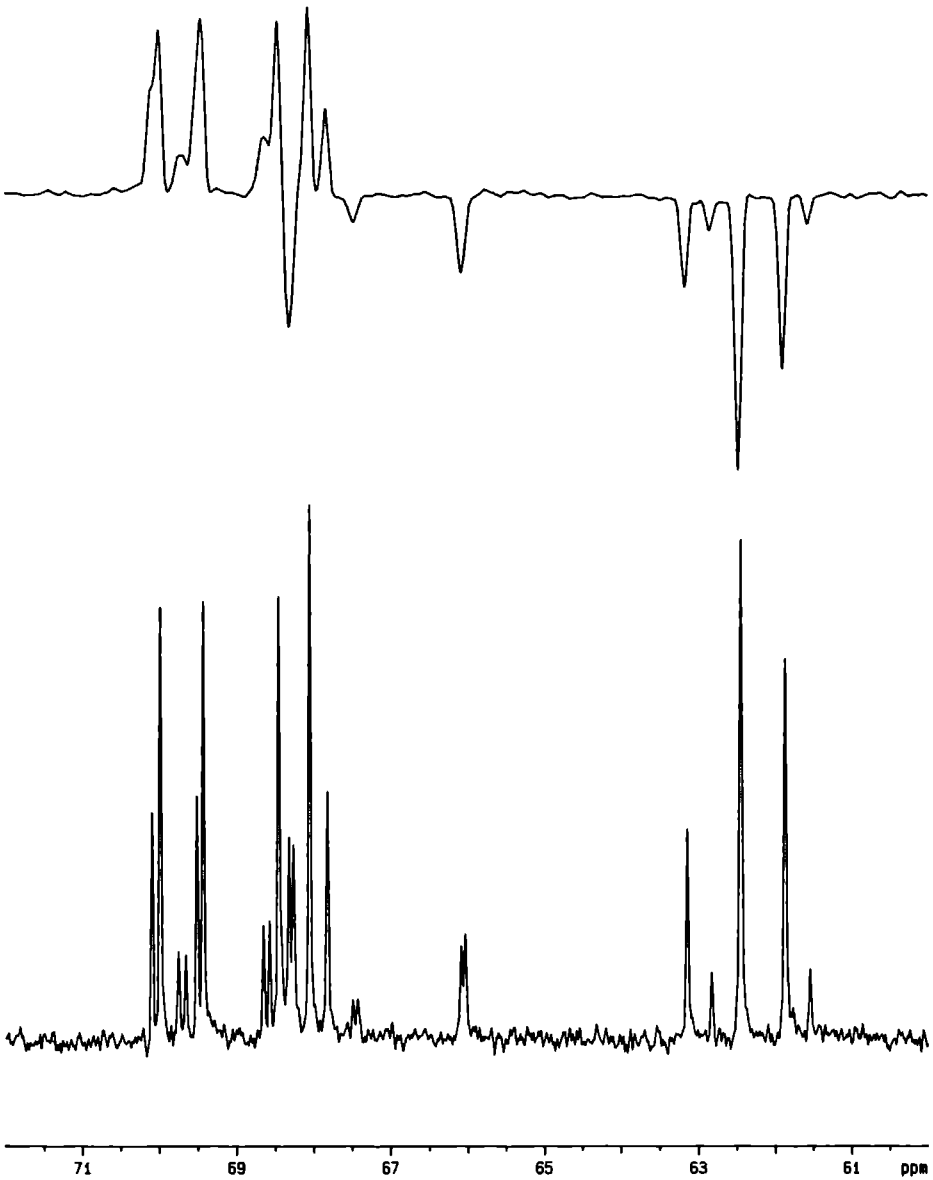


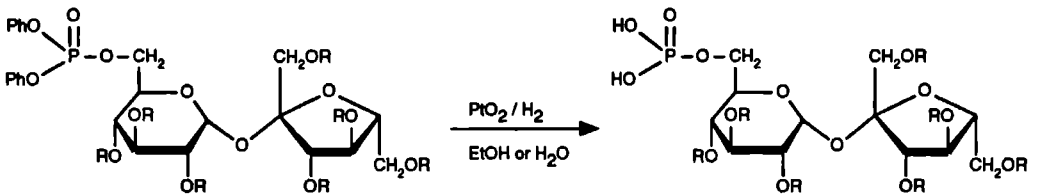
Figure 2 The DEPT-135 (upper) and regular (lower) ^{13}C-NMR spectrum (δ 61-71 ppm) of **39**, **40** and **41**.



The ^{13}C-NMR spectrum (DEPT-135) (Figure 2) in the region of 66-69 ppm exhibited three different signals (68.3, 67.4 and 66.1 ppm) arising from secondary carbons, which appeared at a relatively lower field than usual (61-63 ppm). These three signals each appeared as doublets, due to the coupling with the phosphorus atom, which further indicated that the three signals must arise from the secondary carbons of the three different isomers which are substituted at the C-6, C-6' and C-1' position, respectively.

It can be concluded from these results that under these conditions phosphorylation of sucrose with **32** occurs preponderantly at the primary positions of C-6 and C-6' in almost equal extent, followed by the sterically more hindered C-1' position to a much lesser extent. This group has a neopentyl-like character which could account for its lower activity.

Scheme 3 *Catalytic hydrogenolysis of diphenylphosphate esters of **1**.*



R = H or R = Ac

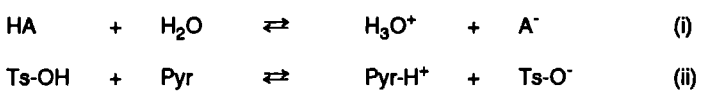
The diphenylphosphoryl-*O*-sucrose hepta-acetate mixture, presumably compounds **39**, **40** and **41**, was subjected to catalytic hydrogenolysis in the presence of PtO_2[53] to yield a mixture of the deprotected phosphates **33**, **34** and **35** in quantitative yield. Treatment of the phosphates after the hydrogenolysis with cyclohexylamine, followed by evaporation, did not unfortunately give crystalline material, but afforded syrups. Several further attempts were made to isolate these mono-phosphates as the corresponding barium salts. The isolated materials were not sufficiently homogeneous to obtain acceptable elemental analyses. It is known that the elemental analyses of cyclohexylamine and barium salts of various sugar phosphate esters do not always conform with the theoretical values[52]. Treatment of the material obtained by catalytic hydrogenolysis in aqueous ethanol of the mixture of **36**, **37** and **38** in the presence of barium carbonate (1 equiv) afforded an amorphous solid. The elemental analysis of this product showed the correct ratio of carbon and hydrogen atoms although the individual percentages were too high.

It can be concluded that the synthesis of several diphenylated phosphates of sucrose is possible. Their subsequent deprotecton by catalytic hydrogenolysis can be performed but the isolation of stable phosphate compounds remains particularly difficult to achieve.

2.4 Cyclic acetals of sucrose

Cyclic acetals of sucrose (as discussed in section 2.1.4) are promising intermediates for the synthesis of various useful derivatives of sucrose, but are difficult to obtain in high overall yields because of the known susceptibility of the interglycosidic bond to acid hydrolysis. Irrespective of the type of acetalation procedure used, *i.e.* by direct or by trans-acetalation, the presence of an acid catalyst is necessary. Therefore, the use of alternative milder acid catalysts such as pyridinium *p*-toluenesulphonate (PPTS) was considered. Crystalline pyridinium *p*-toluenesulphonate is a weakly acidic salt which can catalyse some[59] acetalation and deacetalation reactions, but has previously found limited[60] application in carbohydrate chemistry. An even milder alternative form of this salt, which can be prepared *in situ* using catalytic amounts of *p*-toluenesulphonic acid in a large excess of pyridine, was also investigated as an alternative. In this respect the protonated pyridinium ion (pyr-H^+, ii) can be formally equated with the hydrated proton in the more conventional Brønsted-Lowry equilibrium (i) of a protic acid (Scheme 4).

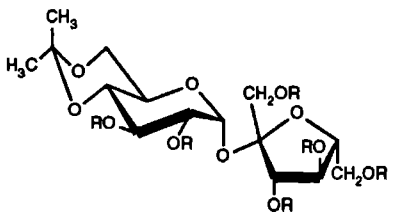
Scheme 4



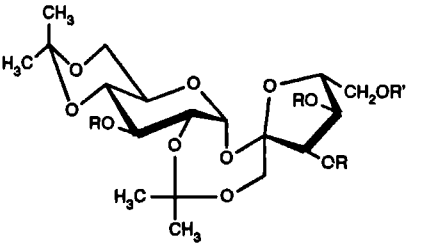
It was thought that the conjugate pyr-H^+ ion in pyridine solution would have sufficient mobility of proton migration between other pyridine molecules for it to act as a very mild acid catalyst, without causing hydrolysis of the glycosidic bond of sucrose. It has been demonstrated that *p*-toluenesulphonic acid in pyridine is an effective system to promote the DCC-mediated esterification of primary and secondary alcohols, whilst simultaneously surpressing *N*-acylurea formation[56]. The relative acidities of several organic acids have been compared[57] in pyridine and water. Most aromatic acids and aliphatic monocarboxylic acids maintained the same relative relationship, and most short-chain dicarboxylic acids became stronger in pyridine. Non-carboxylic acids and non-phenolic acids showed a relative increase in acidity in pyridine compared to carboxylic acids. Recently, the useful catalytic effect of *p*-toluenesulphonic acid in pyridine solution has been demonstrated practically in the synthesis of 1,2:5,6-di-*O*-isopropylidene-D-mannitol[58]. The unusual synthesis of this compound resulted during studies of the development of alternative catalyst for acetalation reactions of acid-sensitive substrates.

In an attempt to develop a more simple isopropylidenation system sucrose was treated with a boiling mixture of 2,2-dimethoxypropane (DMP, 14 equivs) and pyridine containing catalytic amounts of *p*-toluenesulphonic acid (5 mol%), followed by subsequent acetylation of the crude products. TLC-analysis of the reaction mixture indicated a mixture of mono and di-substituted cyclic acetals. The acetylated mixture containing the di-*O*-isopropylidene and the mono-*O*-isopropylidene acetals of **1** could be isolated after column chromatography as the main products together with a small amount of sucrose octa-acetate (**25**). By TLC, GLC, and NMR-analysis the isolated

di-*O*-isopropylidene sucrose derivative (18%) was assigned the 2,1':4,6-diacetal structure **10** which was contaminated with a small proportion of the very acid labile tri-acetal derivative **44**. This minor by-product has also been found in the kinetically controlled acetalation reactions of **1** with 2-methoxypropene[39]. The isolated mono-acetal proved to be the known 4,6-*O*-isopropylidene acetal **9**.



9 R = Ac
42 R = H



10 R = R' = Ac
43 R = R' = H
44 R = Ac , R' = $C(OMe)Me_2$

Another approach to the PPTS catalyzed acetalation of sucrose was also investigated using DMF as the solvent. Treatment of **1** in DMF with 2,2-dimethoxypropane in the presence of catalytic amounts of PPTS at room temperature, followed subsequently by acetylation, afforded a mixture of the 1',2:4,6-diacetal **10** and the triacetal derivative **44** as the main products which were isolated by column chromatography in almost equal amounts. In general chromatographic separation of these two compounds is difficult to achieve because of their slight differences in mobility. From these experiments it can be concluded that PPTS mediated acetation reactions of **1** in pyridine or DMF can be used for the preparation of cyclic acetals of sucrose, but the yields are only moderate and do not represent any distinct improvement on the pre-existing methods.

2.5 Concluding remarks

From these investigations it can be concluded that the direct and selective esterification of sucrose still remains difficult to achieve, and in most cases leads to mixtures of differently substituted isomers of sucrose esters in only modest yields. This low selectivity can be explained by the slight differences in reactivity of the various hydroxyl functions of the sucrose molecule.

The selective preparation of sulphonate esters of sucrose was not achieved using D-(+)-camphorsulphonyl chloride. More promising was the synthesis of sulphonate esters from partially acetylated derivatives of sucrose. The substrates were obtained successfully by the iodine catalyzed deacetylation of sucrose octa-acetate in methanol.

The synthesis of sucrose phosphates by direct reaction of sucrose with the sterically hindered diphenyl phosphorochloridate did not lead to the selective preparation of higher substituted sucrose phosphate derivatives. More selectivity was obtained in the mono-phosphorylation of sucrose using a

controlled amount of this reagent. It was found that phosphorylation occurs preponderantly at the primary positions of C-6 and C-6' in almost equal extent (48 and 41%), followed by the sterically more hindered C-1' position to a much lesser extent (11%).

Finally, it may be concluded that the cyclic acetals, which are promising intermediates, can be prepared with the use of the alternative acetalation-system of *p*-toluenesulphonic acid in pyridine solution, but again only in moderate yields.

2.6 Experimental

General methods

Optical rotations were determined with a Perkin-Elmer automatic polarimeter, model 241 MC on 1% solutions at 20^{0}C in the solvents indicated. Thin-layer chromatography (TLC) on pre-coated plates of silica gel (Merck) was performed with dichloromethane/methanol (4/1, v/v, solvent A) or hexane/ethyl acetate (1/1, v/v, solvent B). Detection was affected by spraying with 3% H_2SO_4 in ethanol followed by heating at 140^{0}C. Column chromatography was performed on silica gel 60 or 60H (Merck) with the eluents indicated. GLC was performed with a Hewlett-Packard 5790 gaschromatograph, using a non-polar capillary column (25m, HP-1), a temperature programme from 100-250^{0}C at 15^{0}C/min, followed by 10 min at 250^{0}C (isothermal), and nitrogen as the carrier gas at 2 ml/min. Compounds were identified by co-injection with authentic samples and the percentages composition of the analysed mixtures are all relative. ^{1}H-NMR spectra were recorded on a Varian EM 390 (90 MHz), Bruker AC 100 (100 MHz) or a Bruker AM 400 (400 MHz) spectrometer on solutions in $CDCl_3$ (internal standard Me_4Si) or D_2O. ^{13}C and ^{31}P-NMR spectra were recorded with a Bruker AM 400 spectrometer operating at 100.6 and 162 MHz, respectively, on solutions in $CDCl_3$ (internal Me_4Si) or D_2O (external dioxane at 67.8 ppm for ^{13}C, external TMP for ^{31}P). IR spectra were determined on a Perkin Elmer 298 spectrophotometer. Melting points were determined on a Reichert thermopan microscope and are uncorrected. Elemental analysis were performed on a Carlo Erba Instruments CHNS-O EA 1108 element analyzer. Mass spectra were recorded using a double focussing VG 7070E mass spectrometer. The fast atom bombardment (FAB) technique (xenon atoms) was used and the chemical ionisation (CI) technique with methane as reaction gas. Sucrose purchased from Sigma Chemicals was powdered finely and dried *in vacuo* (80^{0}C, 15 mm) prior to use. Pyridine was distilled from potassium hydroxide.

D-(+)-10-camphorsulphonyl chloride (**17**). A solution of d-(+)-10-camphorsulphonic acid (9.3 g) in thionyl chloride (8.2 ml) was heated under reflux for 15 min, whereron DMF (0.1 ml) was added[41], and the mixture was then heated under reflux for a further 1 h. The cooled mixture was concentrated *in vacuo*, and the crude product recrystallized (hexane/diisopropyl ether) to yield crystalline **17** (7.9 g, 79%), m.p. 65-66^{0}C, $[\alpha]_D$ +31.3^0 ($CHCl_3$); lit.[46] m.p. 66-67^{0}C, $[\alpha]_D$ +32.1^0. IR(KBr) υ_{max} 1740 (C=O), 1365 (SO_2 as), 1170 (SO_2 ss) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 4.27, 3.67 (d, 2x1H, CH_2SO_2), 2.6-1.3 (m, 7H, camphor skeleton), 1.13 (s, 3H, CH_3), 0.93 (s, 3H, CH_3) ppm.

1-Decanesulphonyl chloride (**18**). A mixture of 1-decanesulphonic acid, sodium salt (5.00 g, 20.5 mmol) in thionyl chloride (6 ml) was heated under reflux (15 min), whereon DMF (0.1 ml) was added and the mixture was heated under reflux for a further 1 h. The cooled mixture was concentrated *in vacuo*, the crude residue dissolved in CH_2Cl_2, washed with 10% aqueous NaCl, dried (Na_2SO_4) and concentrated *in vacuo* to afford **18** as a waxy solid (4.90 g, 99%). IR(KBr) υ_{max} 2900 (CH_2), 1375 (SO_2 as), 1160 (SO_2 ss) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.66 (t, 2H, $RC\underline{H}_2SO_2Cl$), 2.05 (m, 2H, $RC\underline{H}_2CH_2SO_2Cl$), 1.28 (m, 14H, $CH_3(C\underline{H}_2)_7CH_2CH_2SO_2Cl$), 0.88 (t, 3H, CH_3) ppm.

Reaction of sucrose (**1**) *with D-(+)-10-camphorsulphonyl chloride* (**17**).

(a) *With 4 equiv.* A solution of **17** (2.51 g, 10.0 mmol, 4 equivs) in dry pyridine (5 ml) was added dropwise over 1 h to a stirred, cooled (0°C) solution of **1** (0.854 mg, 2.47 mmol) in dry pyridine (60 ml) and then set aside at 0°C for a further 17 h. The mixture was treated with ice water (3 ml) and then concentrated *in vacuo*. The crude residue was dissolved in $CHCl_3$ (25 ml), washed successively with 2M HCl (2 x 10 ml), saturated aqueous $NaHCO_3$ (2 x 10 ml), and water (10 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (CH_2Cl_2/MeOH, 95:5) of the solid residue (2 g) gave two product mixtures of camphorsulphonylated sucroses (D.S. 4 and 3; TLC, solvent A). The first product mixture: 66 mg (2.2%) corresponded to a D.S. of 4. The second product mixture: 322 mg (13.2%) corresponded to a D.S. of 3, m.p. 128-132°C, $[\alpha]_D$ +58° ($CHCl_3$). IR(KBr) υ_{max} 3500 (OH), 2960 (CH_2), 1745 (C=O), 1360 (SO_2 as), 1170 (SO_2 ss) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 5.67 (d, 1H, H-1), 4.8-1.3 (m, camphor and sucrose skeleton, unresolved), 1.07 (s, 3H, CH_3), 0.87 (s, 3H, CH_3) ppm. Calculated for $C_{42}H_{64}O_{20}S_3$ (985.11 D.S. 3): C 51.20%, H 6.55%; Found: C 48.72%, H 6.07%.

(b) *With 3 equiv.* A stirred cooled (0°C) solution of **1** (3.42 g, 10.0 mmol) was treated with compound **17** (7.52 g, 30.0 mmol, 3 equivs) in dry pyridine (200 ml) as described in (a). Column chromatography (CH_2Cl_2/MeOH, 95:5) of the solid residue (4 g) gave two product mixtures of camphorsulphonylated sucroses (D.S. 4 and 3; TLC, solvent A). The first product mixture: 560 mg (5%) corresponded to a D.S. of 4, m.p. 131-133°C. IR(KBr) υ_{max} 3500 (OH), 2960 (CH_2), 1735 (C=O), 1360 (SO_2 as), 1170 (SO_2 ss) cm^{-1}. Calculated for $C_{52}H_{78}O_{23}S_4$ (1199.38 D.S. 4): C 52.07%, H 6.55%; Found: C 51.58, H 6.40%. The second product mixture: 1253 mg (12.7%) corresponded to a D.S. of 3, m.p. 122-125°C. IR(KBr) υ_{max} 3500 (OH), 2960 (CH_2), 1735 (C=O), 1355 (SO_2 as), 1170 (SO_2 ss) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 5.67 (d, 1H, H-1), 4.8-1.3 (m, camphor and sucrose skeleton, unresolved), 1.07 (s, 3H, CH_3), 0.87 (s, 3H, CH_3) ppm. Calculated for $C_{42}H_{64}O_{20}S_3$ (985.11 D.S. 3): C 51.20%, H 6.55%; Found: C 49.95%, H 6.43%.

A sample from the product mixture with D.S. of 4 (400 mg, 0.333 mmol) in pyridine (10 ml) was treated with benzoyl chloride (0.5 ml) and after 16 h the reaction mixture was processed in the usual manner, to give a crude product (470 mg, 87%), m.p. 125-127°C (from 2-propanol). IR(KBr) υ_{max} 2960 (CH_2), 1750 (C=O), 1360 (SO_2 as), 1270 (C-O) 1170 (SO_2 ss), 1100 (C-O), 715 (phenyl) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 8.1-7.2 (m, 20H, benzoyl), 5.86 (d, 1H, H-1), 5.0-1.3 (m, camphor and sucrose skeleton, unresolved), 1.05, 1.00, 0.89, 0.82 (s, 24H, CH_3) ppm. From the integration of the

signals of the aromatic protons, and the methyl signals of the camphorsulphonyl groups the D.S. was calculated as 3.8. Calculated for $C_{80}H_{94}O_{27}S_4$ (1615.83 D.S. 4): C 59.47%, H 5.86%; Found: C 57.58%, H 5.60%.

Reaction of sucrose (**1**) *with 1-decanesulphonyl chloride* (**18**). A solution of **18** (2.46 g, 10.2 mmol, 3.5 equivs) in dry pyridine (10 ml) was added dropwise over 1 h to a stirred, cooled (0^0C) solution of **1** (1.00 g, 2.92 mmol) in dry pyridine (100 ml), and then set aside at 0^0C for a further 15 h. The mixture was treated with ice water (5 ml) for 5 min and then poured into ice water and after 3 h concentrated *in vacuo*. The crude residue was acetylated with acetic anhydride (6 ml) and pyridine (15 ml) in the usual manner to give a syrup. Column chromatography (hexane/ethyl acetate, 6:4) of the material (2.6 g) afforded two product mixtures of 1-decanesulphonylated sucroses (D.S. 1 and 2; TLC, solvent B). The first product mixture: 529 mg (18%), ^{1}H-NMR ($CDCl_3$): δ 5.64 (d, 1H, H-1), 5.5-4.0 (m, sucrose skeleton 14H, unresolved), 3.16 (t, 2H, $RC\underline{H}_2SO_2OR$), 2.10 (s, 18H, 6Ac), 1.83 (m, 2H, $RC\underline{H}_2CH_2SO_2OR$), 1.26 (m, 28H, $CH_3(C\underline{H}_2)_7CH_2CH_2SO_2Cl$), 0.87 (t, 3H, CH_3) ppm. From the integration of the signals of the α-alkylsulphonyl protons and the methyl signals of the acetate groups the D.S. was calculated as 2.0. FAB-MS: *m/z* 1025 (M^+ + Na), 943 (M^+ - OAc), 655 (G/F-$(Ds)_2^+$), 493 (G/F-$(Ds)_1^+$), 331 (G/F$^+$), 211 (G/F$^+$ - 2AcOH), 169 (G/F$^+$ - AcOH - Ac_2O). Second product mixture: 599 mg (24%), ^{1}H-NMR ($CDCl_3$): δ 5.72, 5.62 (d, 1H, H-1), 5.5-4.0 (m, sucrose skeleton 14H, unresolved), 3.17 (t, 2H, $RC\underline{H}_2SO_2OR$), 2.10 (s, 21H, 7Ac), 1.85 (m, 2H, $RC\underline{H}_2CH_2SO_2OR$), 1.27 (m, 14H, $CH_3(C\underline{H}_2)_7CH_2CH_2SO_2Cl$), 0.88 (t, 3H, CH_3) ppm. From the integration of the signals of the α-alkylsulphonyl protons and the methyl signals of the acetate groups the D.S. was calculated as 1.0. FAB-MS: *m/z* 863 (M^+ + Na), 781 (M^+ - OAc), 493 (G/F-$(Ds)_1^+$), 331 (G/F$^+$), 211 (G/F$^+$ - 2AcOH), 169 (G/F$^+$ - AcOH - Ac_2O).

Deacetylation of Octa-O-acetylsucrose (**25**) *with methanol in the presence of iodine.*

A stirred solution of **25** (2000 mg, 2.94 mmol) in methanol (50 ml) was treated with iodine (20 mg, 0.08 mmol, 0.025 equivs) and the mixture was heated under reflux for 40 h. The cooled mixture was treated with solid sodium thiosulphate until colourless, filtered and concentrated *in vacuo* to give a colourless syrup. Column chromatography (hexane/ethyl acetate, 1:2) of the crude product (1.9 g) afforded a fraction containing a hepta-*O*-acetylsucrose, and a fraction composed of a hexa-*O*-acetylsucrose, each as colourless syrups.

Hepta-O-acetylsucrose. A syrup (236 mg, 13%). TLC-analysis: R_f 0.6 (CH_2Cl_2 / MeOH, 9:1). $[\alpha]_D$ $+51^0$ ($CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 5.70 (d, 1H, H-1), 5.5 (m, 2H, H-3', H-3), 5.09 (t, 1H, H-4), 4.92 (dd, 1H, H-2), 2.1 (s, 21H, 7Ac).

Hexa-O-acetylsucrose. A syrup (370 mg, 21%). TLC-analysis: R_f 0.4 (CH_2Cl_2 / MeOH, 9:1). $[\alpha]_D$ $+64^0$ ($CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 5.63 (d, 1H, H-1), 5.48 (t, 1H, H-3), 5.02 (t, 1H, H-4), 4.91 (dd, 1H, H-2), 2.1 (s, 21H, 7Ac).

Synthesis of Octa-O-acetylsucrose (**25**). A stirred suspension of **1** (1000 mg, 2,92 mmol) in acetic anhydride (10 ml) was treated with iodine (70 mg, 0.28 mmol, 0.1 equiv) at room temperature for 16 h, whereon a clear solution was obtained. The mixture was poured into ice water with a portion of

saturated aqueous sodium thiosulphate whereon a white solid crystallized. The crude product was washed several times with water and dried *in vacuo* (1057 mg, 53%), m.p. 85-87^{0}C, $[\alpha]_D$ +62^0 ($CHCl_3$); lit.[55] m.p. 89^{0}C, $[\alpha]_D$ +60^0. A sample from the crude product was recrystallized from 95% ethanol to give **25** with m.p. 86-87^{0}C and $[\alpha]_D$ +60^0. ^{1}H-NMR ($CDCl_3$): δ 5.69 (d, 1H, H-1), 5.44 (m, 2H, H-3', H-3), 5.37 (t, 1H, H-4'), 5.08 (t, 1H, H-4), 4.88 (dd, 1H, H-2), 2.1 (s, 24H, 8Ac).

p-Toluenesulphonylation reactions.

(a) *With hepta-O-acetylsucrose.* A solution of hepta-*O*-acetylsucrose (236 mg, 0.37 mmol) in pyridine (3 ml) was treated with *p*-toluenesulphonyl chloride (200 mg) at 0^{0}C. The mixture was maintained at room temperature for 48 h, and then decomposed by addition of water (2 ml). The mixture was then poured into ice water and after 2 h extracted with CH_2Cl_2 (50 ml). The organic layer was washed successively with 2M HCl, saturated aqueous $NaHCO_3$, water, dried (Na_2SO_4) and concentrated *in vacuo* to a colourless syrup (201 mg, 68%). $[\alpha]_D$ +50^0 ($CHCl_3$), lit.[42] $[\alpha]_D$ +49^0 for the 4'-tosylate **30** and $[\alpha]_D$ +51^0 for the 3'-tosylate **31**. ^{1}H-NMR ($CDCl_3$): δ 7.82-7.37 (m, 4H, Ts), 5.63 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 5.41 (m, 2H, H-3', H-3), 5.32 (t, 1H, H-4'), 5.01 (t, 1H, H-4), 4.76 (dd, 1H, H-2), 2.46 (s, 3H, Ts), 2.1 (s, 21H, 7Ac). FAB-MS: *m/z* 813 (M^+ + Na), 791 (M^++ 1), 731 (M^+ - OAc), 443 (F-Ts$^+$), 331 (G^+), 211 (G^+ - 2AcOH), 169 (G^+ - AcOH - Ac_2O).

(b) *With hexa-O-acetylsucrose.* A solution of hexa-*O*-acetylsucrose (370 mg, 0.62 mmol) in pyridine (3 ml) was treated with *p*-toluenesulphonyl chloride (400 mg) at 0^{0}C. The mixture was maintained at room temperature for 48 h, and then decomposed by addition of water (2 ml). The mixture was then poured into ice water whereon a solid precipitated. The crude product was washed several times with water and dried *in vacuo* (463 mg, 83%), $[\alpha]_D$ +52^0 ($CHCl_3$); lit.[42] $[\alpha]_D$ +54^0, lit.[44] $[\alpha]_D$ +52^0 for the 3',4'-di-tosylate **29**. Recrystallization, m.p. 151-153^{0}C (from ethyl acetate / hexane), lit.[42] 150-152^{0}C (from ether). ^{1}H-NMR ($CDCl_3$): δ 7.78-7.37 (m, 8H, 2Ts), 5.62 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 5.4-5.2 (m, 2H, H-4', H-3), 5.18 (d, 1H, H-3'), 4.98 (t, 1H, H-4), 4.77 (dd, 1H, H-2), 2.46, 2.45 (2s, 6H, 2Ts), 2.1 (s, 18H, 6Ac). FAB-MS: *m/z* 925 (M^+ + Na), 903 (M^++ 1), 843 (M^+ - OAc), 555 (F-Ts_2^+), 443 (F-Ts$^+$), 331 (G^+), 211 (G^+ - 2AcOH), 169 (G^+ - AcOH - Ac_2O), 155 (Ts).

Tosylation of **28** obtained by the method of Capek[44]in another experiment[47], afforded the pure 3',4'-di-tosylate **29**, m.p. 152-153^{0}C, $[\alpha]_D$ +51^0 ($CHCL_3$). ^{1}H-NMR ($CDCl_3$): δ 7.80-7.37 (m, 8H, 2Ts), 5.65 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1), 5.39 (t, 1H, H-3), 5.21 (t, 1H, H-4'), 5.17 (d, 1H, H-3'), 5.06 (t, 1H, $J_{4,3}$ 9.9 Hz, H-4), 4.84 (dd, 1H, $J_{2,3}$ 10.4 Hz, H-2), 2.47, 2.46 (2s, 6H, 2Ts), 2.1 (s, 18H, 6Ac).

Reaction of sucrose (**1**) *with diphenyl phosphorochloridate* (**32**).

(a) *With 1 equiv.* A solution of **32** (1343 g, 5.00 mmol, 1 equiv) in dry pyridine (10 ml) was added dropwise over 1 h to a stirred, cooled (0^{0}C) solution of **1** (1714 mg, 5.01 mmol) in dry pyridine (100 ml) maintained under a stream of nitrogen, and then set aside at 0^{0}C for a further 16 h. The mixture was treated with ice water (4 ml) and then concentrated *in vacuo*. Column chromatography (CH_2Cl_2/MeOH, 8:2) of the crude residue afforded a diphenylphosphorylated sucrose, corresponding to a D.S. of 1 (TLC, solvent A) as a foamy solid (807 mg, 28%), m.p.

113-115^{0}C. IR(KBr) υ_{max} 3300 (OH), 2920 (CH_2), 1590 (C_6H_5), 1270 (P=O), 1190 (POC_6H_5) cm^{-1}. ^{1}H-NMR (D_2O): δ 7.27-7.09 (m, 10H, aromatic), 5.35, 5.20, 5.18 (3d, 1H, H-1), 4.5-1.3.1 (m, sucrose skeleton 13H, unresolved) ppm. ^{31}P-NMR {^{1}H} (D_2O): δ -14.04 (s, 1P), -14.18 (s, 1P), -14.28 (s, 1P) ppm. The relative intensities of the signals were 42, 47 and 11%, respectively. Calculated for $C_{24}H_{31}O_{14}P$ (574.46 D.S. 1): C 50.18%, H 5.44%; Found: C 50.44%, H 5.00%.

(b) *With 3 equiv.* A stirred cooled (0^{0}C) solution of **1** (1.71 g, 5.0 mmol) was treated with compound **32** (4.03 g, 15.0 mmol, 3 equivs) in dry pyridine as described in (a). Column chromatography (CH_2Cl_2/MeOH, 9:1) of the crude residue gave two product mixtures of diphenylphosphorylated sucroses (D.S. 3 and 2, TLC solvent A) as foamy solids. The first product mixture: 1500 mg (29%) corresponded to a D.S. of 3, $[\alpha]_D$ +29.1^0 (CH_2Cl_2). IR(KBr) υ_{max} 3400 (OH), 2960 (CH_2), 1590 (C_6H_5), 1280 (P=O), 1190 (POC_6H_5) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 7.23 (m, 30H, aromatic), 5.5-3.0 (m, sucrose skeleton 19H, unresolved) ppm. From the integration of the signals assigned to the aromatic protons and those of the remaining sucrose protons the D.S. was calculated as 2.9. The second product mixture: 640 mg (16%) corresponded to a D.S. of 2, $[\alpha]_D$ +34.0^0 (CH_2Cl_2). From the integration of the signals in the ^{1}H-NMR spectrum the D.S. was calculated as 2.1.

(c) *With 4 equiv.* A stirred cooled (0^{0}C) solution of **1** (1.71 g, 5.0 mmol) was treated with compound **32** (5.37 g, 20.0 mmol, 4 equivs) in dry pyridine as described in (a). Column chromatography (CH_2Cl_2/MeOH, 9:1) of the crude residue gave three product mixtures of diphenylphosphorylated sucroses (D.S. 5, 3 and 2, TLC solvent A) as foamy solids. The first product mixture: 268 mg (4%) corresponded to a D.S. of 5. IR(KBr) υ_{max} 3400 (OH), 2960 (CH_2), 1590 (C_6H_5), 1280 (P=O), 1190 (POC_6H_5) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 7.23 (m, 50H, aromatic), 5.5-3.0 (m, sucrose skeleton 17H, unresolved) ppm. From the integration of the signals of the aromatic protons and of the sucrose protons the D.S. was calculated to be 4.8. The second product mixture: 942 mg (18%) corresponded to a D.S. of 3. From the integration of the signals in the ^{1}H-NMR spectrum the D.S. was calculated as 2.9. A third product mixture: 434 mg (11%) corresponded to a D.S. of 2 (calculated from the integration of the signals in the ^{1}H-NMR spectrum). Calculated for $C_{36}H_{40}O_{17}P_2$ (806.62 D.S. 2): C 53.61%, H 5.00%; Found: C 52.05%, H 4.83%.

*Diphenylphosphoryl-O-sucrose hepta-acetate (**39**, **40** and **41**).* Treatment of **1** (1709 mg, 5.00 mmol) in pyridine (100 ml) with **32** (1343 g, 5.00 mmol, 1 equiv) as described above in a), followed by acetylation of the foamy product (1040 mg, 36%), m.p. 112-114^{0}C, $[\alpha]_D$ +35.1^0 (MeOH), in the usual manner yielded a mixture of **39**, **40** and **41** as a colourless syrup (1130 mg, 75%). ^{1}H-NMR ($CDCl_3$): δ 7.32-7.24 (m, 10H, aromatic), 5.70, 5.63, 5.58 (3d, 1H, H-1 of 1', 6' and 6-isomer), 5.5-5.3 (m, 3H, H-3, H-4', H-3'), 5.13, 5.07, 5.03 (3t, 1H, H-4), 4.92, 4.86, 4.72 (3dd, 1H, H-2 of 1', 6 and 6'-isomer), 4.6-4.1 (m, 8H, H-5, H-6_{ab}, H-$1'_{ab}$, H-5', H-$6'_{ab}$), 2.1 (s, 21H, 7Ac) ppm. From the integration of the signals of the diphenyl group and of the acetate groups the D.S. was calculated as 1.0. From the integration of the signals from H-1 and H-2 the distribution of the 6-, 6'- and 1'-substituted isomers was calculated as 48, 41 and 11%, respectively. Irradiation of the H-2 signal from the 6'-isomer at 5.72 ppm caused the doublet assigned to H-1 at 5.63 ppm to be changed into a

singlet. ^{13}C-NMR (DEPT-135, $CDCl_3$): δ 170.0-169.1 (C=O acetyl), 150.24 (d, q-C phenyl, J_{PC} 6.0 Hz), 129.71, 125.38, 120.00 (phenyl), 103.91 (C-2), 89.93 (C-1), 79.52, 75.34, 74.69, 69.99, 69.42, 68.42, 68.04 (C-5', C-3', C-4', C-2, C-3, C-5, C-4), 68.28, 67.37, 66.05 (3d, C-6, C-1' and C-6' of 6, 1' and 6'-isomer, $^2J_{POC}$ 5.0 Hz) 63.14, 62.82, 62.45 (d), 61.87 61.45 (C-6', C-1', C-6), 20.5 (CH_3 acetyl) ppm. ^{31}P-NMR ($CDCl_3$): δ -14.16 (t, 1P), -14.32 (t, 1P), -14.55 (t, 1P), triplets changed into singlets in the proton decoupled spectrum. CI-MS: *m/z* 869 (M^+ + 1), 809 (M^+ - OAc), 619 (M^+ - DPP) 521 (G/F-(DPP)$^+$), 331 (G/F$^+$), 211 (G/F$^+$ - 2AcOH), 169 (G/F$^+$ - AcOH - Ac_2O).

In another experiment an alternative manner of processing was used. A stirred cooled (0^0C) solution of **1** (1.71 g, 5.0 mmol) was treated with compound **32** (1.71 g, 5.0 mmol) in dry pyridine as described above. The crude product was dissolved in n-butanol (50 ml), washed successively with 2M HCl, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried ($NaSO_4$) and concentrated *in vacuo* to a syrup. The crude residue was acetylated with acetic anhydride and pyridine in the usual manner to give a mixture of **39**, **40** and **41** as a syrup (1360 mg, 31%). ^{1}H-NMR ($CDCL_3$): δ 7.23 (m, 10H, aromatic), 5.6 (d, 1H, H-1), 5.5-4.1 (m, sucrose skeleton 13H, unresolved), 2.1 (s, 21H, 7Ac) ppm.

Catalytic hydrogenolysis of diphenylphosphoryl-O-sucrose hepta-acetate (39, 40 and 41). A solution of the mixed acetates **39**, **40** and **41** (476 mg, 0.55 mmol) in ethanol (50 ml) was treated with PtO_2 (75 mg) and the mixture was hydrogenated (1 atm) for 6 h at room temperature. The inorganic material was removed by filtration, washed with ethanol, and the combined filtrate and washings were treated with a further amount of PtO_2 (75 mg), and hydrogenation was continued for a further 4 h. The inorganic material was removed by filtration, then washed with ethanol (2x10 ml) and the combined filtrate and washings were concentrated *in vacuo* to yield the mixture of **33**, **34** and **35** as a colourless oil (313 mg, 99%). ^{1}H-NMR ($CDCl_3$): δ 5.6 (d, 1H, H-1), 5.5-4.1 (m, sucrose skeleton 13H, unresolved), 2.1 (s, 21H, 7Ac) ppm. ^{31}P-NMR {^{1}H} ($CDCl_3$): δ -1.9 ppm.

Catalytic hydrogenolysis of diphenylphosphoryl-O-sucrose hepta-acetate (39, 40 and 41) followed by treatment with cyclohexylamine. A solution of compounds **39**, **40** and **41** (265 mg, 0.31 mmol) in aqueous ethanol was subjected to hydrogenolysis for 5h as described above. The ethanolic solution of the crude product obtained was treated with cyclohexylamine (0.07 ml, 2 equivs). No crystallization occurred, and concentration *in vacuo* of the mixture followed by treatment with ether and then concentration *in vacuo* afforded a syrup (284 mg, 96%). ^{1}H-NMR ($CDCl_3$ + D_2O): δ 5.60 (d, 1H, H-1), 5.5-4.1 (m, 13H, sucrose skeleton), 2.90 (m, 2H, N-CH), 2.1 (s, 21H, 7Ac), 1.76 (m, 8H, CH_2), 1.29 (m, 12H, CH_2) ppm.

Catalytic hydrogenolysis of diphenylphosphoryl-O-sucrose (36, 37 and 38) in the presence of barium carbonate. A solution of compounds **36**, **37** and **38** (431 mg, 0.75 mmol) in aqueous ethanol was subjected to hydrogenolysis for 6h as described above but in the presence of $BaCO_3$ (155 mg, 0.78 mmol). Further hydrogenolysis in water for 4 h as described above afforded after processing and drying *in vacuo* the barium phosphate ester of **1** as an amorphous white solid (416 mg, 99%). Calculated for $C_{12}H_{21}BaO_{14}P$ (557.60): C 25.9%, H 3.8%, (ratio 6.8:1); Found: C 31.9%, H 4.8%. (ratio 6.7:1).

Reaction of sucrose (**1**) *in pyridine with 2,2-dimethoxypropane and catalytic amounts of p-toluenesulphonic acid.*

A solution of **1** (2010 mg, 5.87 mmol) in dry pyridine (100 ml) was treated with 2,2-dimethoxypropane (10 ml, 14 equivs) in the presence of *p*-toluenesulphonic acid (55 mg, 5 mol%) and the mixture was heated under reflux for 5 h. The solution was then neutralized with IR-45(HO^-) resin , filtered and concentrated *in vacuo*. The syrupy residue was treated with acetic anhydride (13 ml) and pyridine (30 ml) in the usual manner to give a syrup. Column chromatography (hexane/ethyl acetate, 1:1) of the material (3.5 g) afforded the di-*O*-isopropylidenesucrose tetra-acetate **10** as a foamy solid (611 mg, 18%); $[\alpha]_D$ $+15^0$ ($CHCl_3$), lit.[39] $[\alpha]_D$ $+13^0$. GLC analysis: R_t 17.27 (65%), 17.92 (15% of **44**). ^{1}H-NMR ($CDCl_3$): δ 6.08 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 5.47 (dd, 1H, H-4'), 5.30 (t, 1H, H-3), 5.14 (d, 1H, H-3'), 3.80 (dd, 1H, H-2), 3.6-3.7 (1H, H-4), 2.0-2.2 (s, 12H, 4Ac), 1.45, 1.44, 1.39, 1.26 (s, 12H, 4Me). ^{13}C-NMR ($CDCl_3$): δ 170.5-170.0 (C=O acetyl), 104.5 (C-2), 101.4 (qC, 1'-2 acetal), 99.6 (qC, 4-6 acetal), 91.4 (C-1), 79.6, 75.7, 73.8, 71.7, 71.4, 70.5, 66.3 (C-5', C-3', C-4', C-2, C-3, C-5, C-4), 65.1, 64.3, 62.0 (C-6', C-1', C-6), 29.0, 18.9 (2Me, 4-6 acetal), 25.4, 23.8 (2Me 1'-2 acetal), 20.7 (CH_3 acetyl) ppm. CI-MS: *m/z* 591 (M^+ + 1), 533 (M^+ - $OC(Me)_2$), 472 (M^+ - 2OAc). Further elution afforded the 4,6-*O*-isopropylidenesucrose hexa-acetate **9** (347 mg, 9.3%). $[\alpha]_D$ $+51^0$ ($CHCl_3$), lit.[39] $[\alpha]_D$ $+46^0$. GLC analysis: R_t 19.62 (85%). ^{1}H-NMR ($CDCl_3$): δ 5.63 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1), 5.43 (d, 1H, H-3'), 5.35 (m, 2H, H-4', H-3), 4.82 (dd, 1H, H-2), 3.6-3.7 (1H, H-4), 2.0-2.2 (s, 18H, 6Ac), 1.47, 1.38 (s, 6H, 2Me). ^{13}C-NMR ($CDCl_3$): δ 170.5-169.7 (C=O acetyl), 104.0 (C-2), 99.7 (qC, 4-6 acetal), 90.4 (C-1), 79.2, 75.6, 74.9, 71.7, 71.1, 69.1, 64.5 (C-5', C-3', C-4', C-2, C-3, C-5, C-4), 63.4, 63.1, 61.8 (C-6', C-1', C-6), 29.0, 18.9 (2Me, 4-6 acetal), 20.7 (CH_3 acetyl) ppm. CI-MS: *m/z* 635 (M^+ + 1), 575 (M^+ - OAc), 533 (M^+ - OAc - $OC(Me)_2$), 516 (M^+ - 2OAc), 331 (F^+), 211 (G/F^+ - 2AcOH), 169 (G/F^+ - AcOH - Ac_2O).

Reaction of sucrose (**1**) *in DMF with 2,2-dimethoxypropane and catalytic amounts of pyridinium p-toluenesulphonate.* A stirred suspension of **1** (3 g, 8.8 mmol) in dry DMF (80 ml) was treated with 2,2-dimethoxypropane (11 ml, 10 equivs) in the presence of pyridinium *p*-toluenesulphonate (85 mg, 4 mol%) at room temperature for 48 h whereon a clear solution was obtained. The solution was then neutralised with NaOAc, filtered and concentrated *in vacuo*. The syrupy residue was treated with acetic anhydride and pyridine in the usual manner to give a syrup. Column chromatography (hexane / ethyl acetate, 1:1) of a sample (2 g) of the above crude product (5 g) afforded compound **44** as a syrup (215 mg, 0.35 mmol). GLC analysis: R_t 18.18 (65%). ^{1}H-NMR ($CDCl_3$): δ 6.06 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 5.6-5.2 (3H, H-4', H-3, H-3'), 4.4-3.4 (m, 10H), 3.2 (3H, OMe), 2.0-2.2 (s, 9H, 3Ac), 1.2-1.5 (18H, $3CMe_2$). Further elution afforded a mixture of **44** and **10** (488 mg) and finally 1',2:4,6-di-*O*-isopropylidenesucrose tetra-acetate **10** (137 mg, 0.23 mmol). $[\alpha]_D$ $+14^0$ ($CHCl_3$), lit.[39] $[\alpha]_D$ $+13^0$; m.p. 135-136°C (from diisopropylether), lit.[39] 136-137°C. GLC analysis: R_t 17.28 (89%). ^{1}H-NMR spectrum as above. Calculated for $C_{26}H_{38}O_{15}$ (590.56): C 52.88%, H 6.49%; Found: C 53.09%, H 6.51%.

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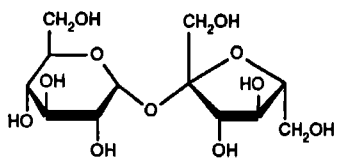
IODINE-CATALYZED ACETALATION REACTIONS OF SUCROSE AND SOME RELATED COMPOUNDS - A NOVEL CLEAVAGE-ISOPROPYLIDENATION METHOD#

3.1 Introduction

The conventional acid-catalyzed isopropylidenation of sucrose (**1**) has been studied severally[1]. Interglycosidic bond cleavage leading to the formation of acetals of D-glucose and D-fructose has invariably resulted. The monoacetal **2** and diacetal **3** were prepared eventually by acid-catalyzed exchange between **1** and 2,2-dimethoxypropane[2,3] or 2-methoxypropene[4]. Prolonged treatment at higher catalyst concentrations causes glycosidic bond fission, and several unusual acetals of D-glucose and methyl α-D-fructofuranoside have been isolated and characterized[5].



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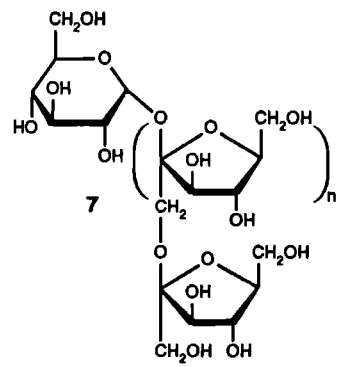

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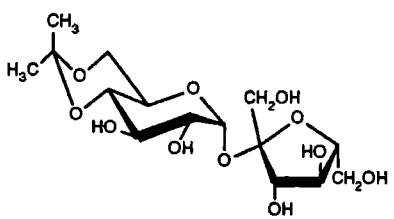

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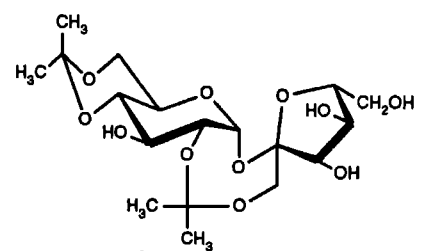
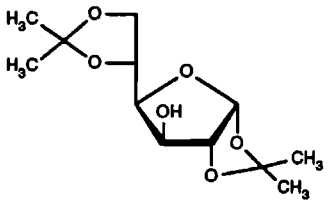


3

As part of recent studies[6] of the development of new mild catalysts for the acetalation of acid-sensitive substrates, sucrose (**1**) was treated with iodine in boiling acetone. Very efficient cleavage of the interglycosidic bond with concomitant isopropylidenation occurred to yield the diacetals **4**, **5**, and **6**. The related fructofuranosyl-containing oligosaccharides inulin (**7**), and

raffinose (**8**), their constitutional monosaccharide units, D-fructose, D-galactose and D-glucose, and some common disaccharides were then treated under similar conditions. The results of this study and some related aspects are described in this chapter.



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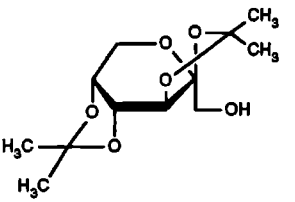

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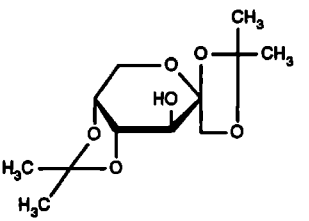

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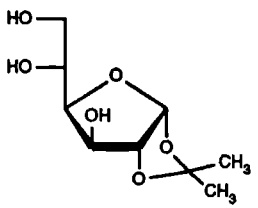

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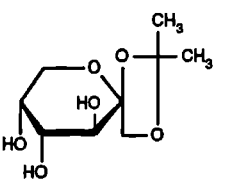

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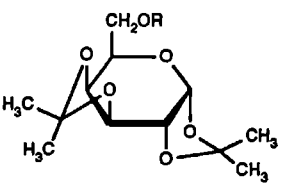


11 R = H
17 R = Ts

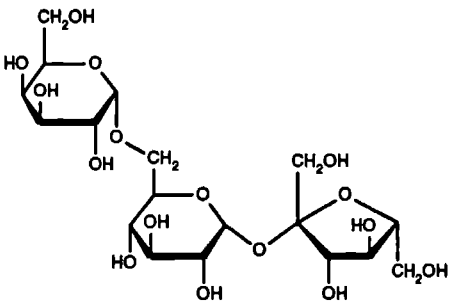
3.2 Results and discussion

When sucrose (**1**) was treated with a catalytic amount of iodine in boiling acetone for 4 h three products were yielded (TLC, solvent B). Further analysis (GLC) of the crude product mixture identified these as the di-*O*-isopropylidene compounds **4** (47%), **5** (37%) and **6** (11%). They were the only products produced and there appeared to be no remaining unreacted compound **1** in the mixture (TLC, solvent A).

Treatment of this mixture with 80% aqueous acetic acid, followed by selective ether extraction, yielded pure monoacetal **9**; compounds **5** and 1,2-*O*-isopropylidene-β-D-fructopyranose (**10**), resulting from the partial acid hydrolysis of **6**, were separated by fractional recrystallization. Compounds **5** and **9**, isolated directly, were sufficiently pure (GLC) for use as synthetic intermediates without further purification. These acetals have been obtained[7,8] previously from **1**, but the procedures described involve several tedious isolation and purification steps. The method described here represents an improved direct route which could be important for future large scale use of sucrose (**1**).

In view of this observed facile cleavage-acetalation sequence, attention was directed towards the treatment of inulin (**7**) under similar conditions. There has been considerable interest expressed recently[9] in **7** as a potential raw material for the production of *inter alia* D-fructose, ethanol,

2,3-butanediol, D-mannitol, glycerol, 5-(hydroxymethyl)-2-furaldehyde and laevulinic acid. Some of these proposals must be considered still speculative, but its use in medicine and food technology is established. The chemistry of **7** merits further study.



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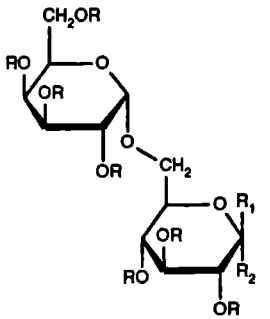
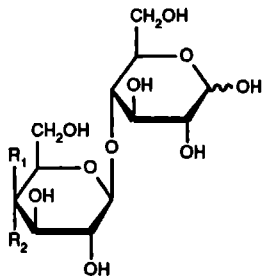
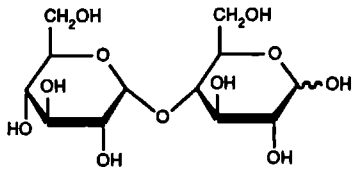


12 R = Ac, R_1 = OAc, R_2 = H
13 R = H, R_1 = H, R_2 = OH



14 R_1 = H, R_2 = OH
16 R_1 = OH, R_2 = H



15

Thus, treatment of a stirred suspension of **7** in boiling acetone with a catalytic amount of iodine produced a clear solution after 16h. Analysis (GLC) of the mixture revealed compound **5** (88%) and compound **6** (12%); pure compound **5** (58%) was isolated from the crude product (81%) by direct recrystallization. Diacetal **4** was not identified as a component of the product mixture. The D-glucose content of **7** varies between approximately 1.5 and 5% depending on the source and analytical procedure[10].

Conventional acid-catalyzed isopropylidenation of **7** was found[11] not to be a convenient source of the acetals **5** and **6**. Long reaction times (4-7 days) were required for the hydrolysis-isopropylidenation sequence during which considerable degradation and formation of coloured by-products was observed. The combined yields of **5** and **6** were not high (ca. 45%), and the product mixtures were difficult to purify. The known[12] acid-catalyzed formation of D-fructose anhydrides from **7**, and the complex series of reactions that D-fructose undergoes when treated with

acid probably attributed to the complexity of this system[11,12].

When raffinose (**8**), another common fructofuranosyl containing tri-saccharide, was treated under identical conditions with acetone and iodine for 72h compounds **4** (27%), **5** (37%), **6** (4%) and 1,2:3,4-di-*O*-isopropylidene-D-galactose (**11**, 28%) were identified (GLC) as the reaction products. No attempt was made to separate these compounds from the crude syrupy product, which was obtained in 84% yield.

Treatment of **8** in the same way, but for only 6h, followed by acetylation of the insoluble portion of the crude reaction product yielded β-D-melibiose octaacetate (**12**, 46%). The parent disaccharide **13** is normally[13] prepared by fermentation of **8** with top yeast (baker's yeast). During fermentation the sucrose type linkage is cleaved by the invertase present forming **13** and D-fructose. The method described here represents a simple alternative, albeit in lower yield.

The formation of **11** from **8** suggested that the cleavage reaction may not be restricted to only non-reducing fructofuranosyl linkages. It was decided therefore to investigate the effects of the reagent combination on a number of common disaccharides containing only pyranosyl linkages. D-Melibiose (**13**), D-cellobiose (**14**), D-maltose (**15**) and D-lactose (**16**) were chosen as models. The results of these experiments are depicted in Table 1.

Table 1 Reactivity of disaccharides with I_2 - acetone.

Substrate	% substrate recovered	Products		
		compound	composition[a]	% yield
D-Melibiose (**13**)	54	**4** + **11**	43 : 34	27
D-Cellobiose (**14**)	94	-	-	-
D-Maltose (**15**)	64	**4**	68	16
D-Lactose (**16**)	66	**4** + **11**	39 : 24	16

a) Determined by GLC.

The observed order of reactivity parallels that for the normal acid-catalyzed hydrolysis of these saccharides[14], but with a much lower degree of cleavage. The relatively high reactivity of **13** was not unexpected in view of the result obtained with raffinose (**8**). The results indicate that the majority of pyranosyl linkages would probably be unaffected by the mixture under the usual reaction conditions *i.e.* low catalyst concentration and short reaction times. The reaction of other glycopyranosides could be investigated further.

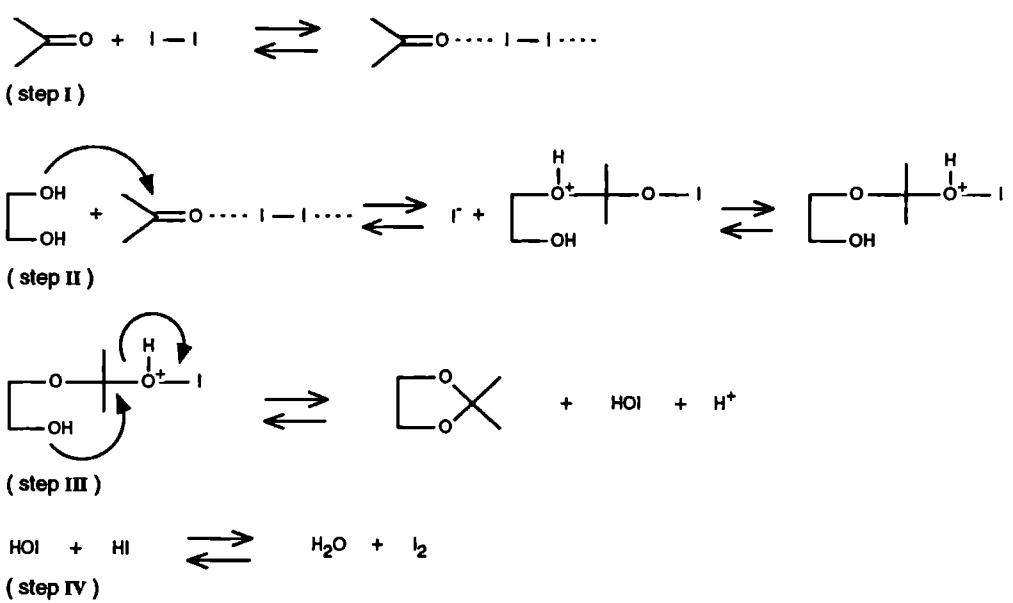
Iodine is a recognized[15] catalyst or reagent in organic chemistry, but has not previously found wide application in carbohydrate chemistry. The cleavage of **1** by iodine in *N,N*-dimethylformamide

at 100°C to yield 5-(hydroxymethyl)-2-furaldehyde has been reported[16]. The reaction was restricted to the released D-fructose unit. D-Glucose was recovered essentially unchanged, and no degradation occurred in the absence of iodine. A mechanism involving the generation of a carbocation on D-fructofuranose, followed by a series of dehydration steps, was proposed.

Another reaction in carbohydrate chemistry involving the use of iodine is the iodonium-mediated glycosidation of "armed" or "disarmed" alkyl 1-thioglycosides for the introduction of 1,2-*cis* or *trans* interglycosidic linkages in the synthesis of some specific disaccharides[17]. Treatment of an "armed" thioglycoside (protected with benzyl groups) with a disarmed thioacceptor (protected with benzoyl groups), in the presence of iodonium dicollidine perchlorate (IDCP) gave predominantly 1,2-*cis* disaccharides. Glycosidation of an appropiate methylglycoside acceptor by a fully benzoylated ethyl 1-thioglycoside with *N*-iodosuccinimide (NIS) and catalytic triflic acid afforded 1,2-*trans* disaccharides exclusively.

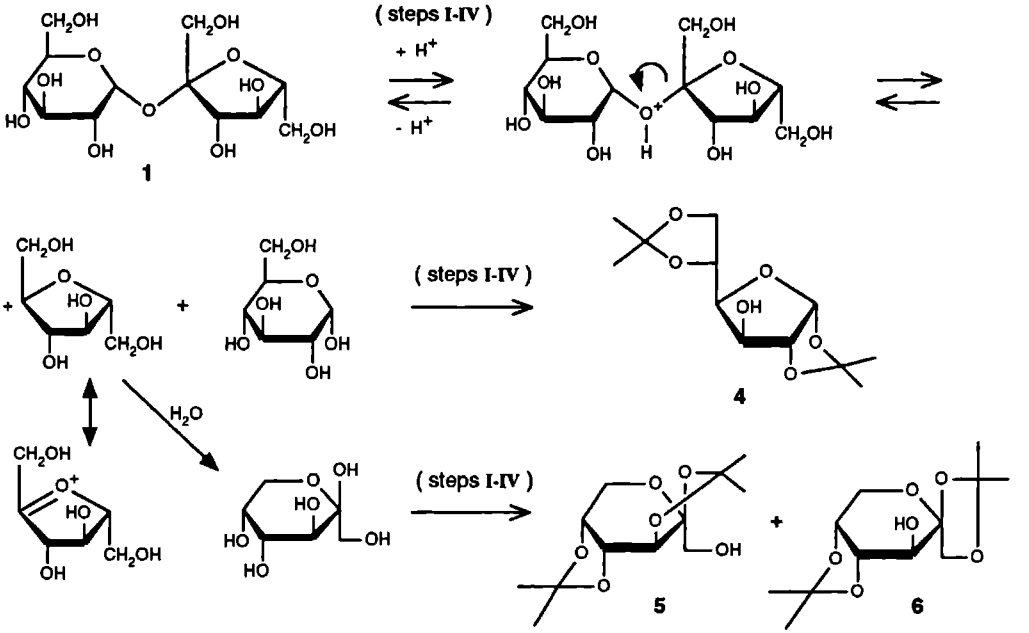
Iodine has also been proposed as a catalyst for the isopropylidenation of some simple monosaccharides and sugar alcohols with acetone[18]. The amount of iodine employed (300 mg/g substrate) seems excessive in view of its earlier reported[19,20] uses as a dehydrating and condensing agent. Carbohydrate acetals and dithioacetals are cleaved[21] by dilute solutions of iodine in methanol. The product mixtures are composed mainly of furanoside mixtures approximating to the early stages of conventional acid catalyzed methanolysis. Simple glycosides and disaccharides, including some sucrose derivatives, are unaffected under the conditions which may be considered more forcing than those employed in the current study.

Scheme IA *Proposed mechanism for the iodine catalyzed isopropylidenation of diol groups.*



The mechanism of the reactions described herein probably occur by two closely associated processes. The sequences are initiated by the formation of an acetone-iodine addition complex[22] followed by the partial or complete acetalation of suitable vicinal diol groups (Scheme 1A). This leads to the subsequent generation of mildly acidic conditions which are sufficient to cause cleavage of acid sensitive glycosidic bonds. The facile and mild acid hydrolysis of sucrose (**1**)[23], and related saccharides, occurs by the collapse of an oxonium ion to give D-glucose and a D-fructofuranosyl carbocation which reacts further with water to give D-fructose (Scheme 1B). The released monosaccharides then undergo further isopropylidenation by a process which is analogous to the conventional acid-catalyzed reaction.

Scheme 1 *Acid catalyzed hydrolysis of sucrose and isopropylidenation of the released monosaccharides.*



The attention was subsequently directed towards the treatment of the individual monosaccharide structual units of the saccharides used in this investigation, under similar conditions. The yield of the diacetal **4** (71.5%) from D-glucose was particularly gratifying. There are a number[24,25] of well-established syntheses of this well-known derivative, they all involve time consuming neutralization and purification steps. There is frequently the need to remove considerable amounts of unreacted D-glucose and the monoacetal **9** from the product. Compound **4** and **9** are two of the most frequently employed carbohydrate synthons and have found numerous applications in

both carbohydrate and natural product chemistry. They also provide convenient routes to *inter alia* usefully protected derivatives of D-allose[26,27], D-gulose[28], D-ribose[29,30], and D-idose[31]. Compound **4** has recently[32] been employed as an intermediate in syntheses of D-ribulose and D-erythronic acid.

The facile formation of either of the di-*O*-isopropylidene-D-fructopyranose derivatives **5** (81.5%) and **6** (70%), from D-fructose is noteworthy. When the reaction is performed in boiling acetone for 3 h compound **5** is formed, whereas compound **6** is formed using room temperature. Compound **5** is considered to be the thermodynamically-controlled product from the normal acid-catalyzed condensation of D-fructose with acetone, whereas **6** is the kinetic product. The diacetal **6** is formed initially, but isomerizes to **5** at a rate depending upon the catalyst concentration. The use of zinc chloride is reported to favour the formation of **6**. A comprehensive study of the optimal conditions required for the isolation of the two components has been described[33] but it was reported that purification of the crude products by fractional crystallization was not readily achieved. The conditions described here now, *i.e.* using catalytic amounts of iodine in acetone, represent the most convenient reported hitherto.

The conventional acid-catalyzed condensation of acetone with D-galactose provides compound **11** in good yield[34] but the crude product needs to be freed from considerable quantities of acetone condensation products by distillation *in vacuo*. The procedure described now, involving treatment of D-galactose in boiling acetone containing iodine (0.05 equiv), leads to essentially pure material in excellent yield (83.5%), without further purification. The syrupy product was characterized as the known[34] *p*-toluenesulphonate **17** in the usual manner.

For comparitive purposes D-glucose was also treated with acetone containing iodine (0.21 equiv, 0.6% w/v) under the conditions described by Kartha[18]. Although analysis (GLC) of the crude product indicated that the diacetal **4** was present in 77% yield, difficulty was encountered in isolating the pure material (45%) because of the acetone condensation products present. When acetone alone was treated with the same quantity (0.6% w/v) of iodine dark oily material was isolated which on analysis (GLC) was shown to contain at least 11 constituents, whereas only trace amounts of these materials were detected when the lower quantity (0.14% w/v) of iodine was employed.

Further examples of the use of this novel isopropylidenation procedure, and its application to other carbonyl derivatives are presented in chapter 4.

3.3 Experimental

General methods

Optical rotations were determined with a Perkin-Elmer automatic polarimeter, model 241 MC on 1% solutions at 20^{0}C. Thin-layer chromatography (TLC) on pre-coated plates of silica gel (Merck) was performed with dichloromethane - methanol (4/1, v/v, solvent A) or hexane - ethyl acetate (1/1, v/v, solvent B). Detection was affected by spraying with 3% H_2SO_4 in ethanol followed by heating at 140^{0}C. GLC was performed with a Hewlett-Packard 5790 gaschromatograph; a fused silica capillary column (25m) coated with HP-1 cross-linked methyl silicone gumphase operating at

100-150°C, 100°C (isothermal) for 5 min followed by 5°C/min for 10 min, and nitrogen as the carrier gas at 2 ml/min was used. Compounds were identified by co-injection with authentic samples and the percentages composition of the analysed mixtures are all relative. Melting points were determined on a Reichert thermopan microscope and are uncorrected. ^{1}H-NMR spectra were recorded with a Bruker AC 100 (100 MHz) spectrometer on solutions in $CDCl_3$ (internal standard Me_4Si), and were used routinely to identify known products. Inulin, (ex dahlia tubers) purchased from Sigma Chemicals, and sucrose were powdered finely and dried *in vacuo* (80°C, 15 mm) prior to use.

Reaction of acetone containing iodine.

(a) *With sucrose* (**1**). A stirred suspension of sucrose (**1**, 10.0 g, 29.2 mmol) in acetone (500 ml) was treated with iodine (75 mg, 0.3 mmol, 0.01 equiv) and the mixture was heated under reflux for 4 h, whereon a clear solution was obtained. The cooled mixture was treated with 0.5 M aqueous sodium thiosulphate solution until colourless, concentrated *in vacuo*, and the resultant product was dissolved in a mixture of dichloromethane (250 ml) and water (50 ml). The separated organic layer was washed with water (2 x 100 ml), 10% aqueous sodium chloride solution (100 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give a colourless oil (14.44 g) which crystallized on standing.

The crude product was dissolved in 80% aqueous acetic acid (200 ml), set aside at room temperature for 22 h, and concentrated *in vacuo*. The residue was suspended in ether (100 ml), heated to boiling with stirring, and then stored overnight at 4°C. The resultant solid material (5.12 g, 80%) was collected by filtration, washed with cold ether (25 ml) and recrystallized from diisopropyl ether/ methanol to give 1,2-*O*-isopropylidene-α-D-glucofuranose (**9**, 4.03 g, 63%), m.p. 161-162°C, $[\alpha]_D$ -11.6° (water); lit.[24] m.p. 160-161°C, $[\alpha]_D^{19}$ -11.4° (water).

The combined filtrate and washings were washed with water (50 ml), dried ($CaCl_2$), concentrated *in vacuo*, and the crude product (5.41 g) was recrystallized from diisopropyl ether/ hexane to yield 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**5**, 3.15 g). Treatment of the mother liquor with petroleum ether, b.p. 80-100°C, yielded more **5** (0.87 g); combined yield (4.02 g, 53%), m.p. 95-96°C, $[\alpha]_D$ -38.5° (acetone); lit.[33] m.p. 97°C, $[\alpha]_D^{25}$ -38.1° (acetone).

The above separated water washings were concentrated *in vacuo* and the crystalline residue recrystallized from diisopropyl ether/ethanol to give the monoacetal **10** (0.22 g, 3.4%), m.p. 122-123°C, $[\alpha]_D$ -160° (water); lit.[35] m.p. 120-121°C, $[\alpha]_D$ -158.9° (water).

The remander of the material in the mother liquor was a mixture of compounds **9** and **10** which were not separated further.

(b) *With inulin* (**7**). A stirred mixture of inulin (**7**, 500 mg) suspended in acetone (50 ml) containing iodine (35 mg, 0.14 mmol, 0.05 equiv) was heated under reflux for 16 h and the resulting clear solution processed as described above in (a). Recrystallization of the crude crystalline product (589 mg, 81%) from diisopropyl ether/ hexane gave pure **5** (419 mg, 58%), m.p. 94-95°C, $[\alpha]_D$ -38.2° (acetone).

(c) *With D-raffinose pentahydrate* (**8**). A stirred suspension of **8** (1.003 g) in acetone (50 ml) containing iodine (21 mg, 0.08 mmol, 0.05 equiv) was heated under reflux for 72 h and processed as described in (a). The resultant pale yellow oil (1.036 g, 84%) was subjected to analysis (GLC), but it was not separated further.

In another experiment **8** (2.973 g, 5 mmol) suspended in acetone (120 ml) containing iodine (45 mg) was heated under reflux with stirring for 6 h. The resultant mixture was cooled to room temperature and the insoluble material was collected by filtration, washed with acetone (2 x 20 ml) and dried *in vacuo* over P_4O_{10}. The dried product (1.82 g) was added in small portions to a boiling mixture of anhydrous sodium acetate (0.5 g) in acetic anhydride (10 ml). On completion of the addition the mixture was maintained at 100^0C for 15 mins, cooled to roomtemperature, poured with stirring into ice water (200 ml) , and stored at 0^0C for 24 h. The water was decanted from the semi-solid material, which was dissolved in dichloromethane (75 ml) and the extract was washed successively with water (20 ml), saturated aqueous sodium hydrogen carbonate (20 ml), and water (10 ml). The dried (Na_2SO_4) washed extract was concentrated *in vacuo* and the residue recrystallized from ethanol to give β-D-melibiose octaacetate (**12**, 1.56 g, 46%), m.p. 173-176^{0}C, $[\alpha]_D$ +102^0 ($CHCl_3$); lit.[13] m.p. 177-178^{0}C, $[\alpha]_D$ +104^0 ($CHCl_3$).

(d) *With D-melibiose* (**13**), *D-cellobiose* (**14**), *D-maltose* (**15**) *and D-lactose* (**16**). The individual disaccharide, monohydrates (1.0 g) suspended in acetone (50 ml) containing iodine (40 mg, 0.05 equiv) were heated under reflux with stirring for 72 h. The resulting mixtures were cooled and the unreacted materials collected by filtration, washed with acetone (20 ml) and dried *in vacuo* (P_4O_{10}). The combined filtrate and washings were processed as described above in (a) and subjected to analysis (GLC). The results of these experiments are reported in table 1. The unreacted portion of the products were characterised by ^{1}H-NMR spectroscopy (D_2O) in the usual manner by comparison with authentic samples of the disaccharides.

(e) *With D-glucose*. D-Glucose (10.0 g, 55.5 mmol) suspended in acetone (500 ml) containing iodine (700 mg, 2.76 mmol, 0.05 equiv) was heated under reflux with stirring for 2 h, and then processed as descibed in (a). Recrystallization (petroleum ether, 80-100^{0}C) of the resultant crude product (12.6 g, 87%) afforded **4** (10.32 g, 71.5%), m.p. 110^{0}C, $[\alpha]_D$ -18.8^0 (water); lit.[24] m.p. 110^{0}C, $[\alpha]_D^{20}$ -19.7^0 (water).

In another experiment treatment of D-glucose with iodine (140 mg, 0.01 equiv) in the same manner, but for 4 h, gave essentially the same result.

(f) *With D-fructose*. A stirred suspension of D-fructose (1.075 g, 5.96 mmol) in acetone (50 ml) containing iodine (71.7 mg, 0.28 mmol, 0.05 equiv) was heated under reflux for 3 h and processed as in (a). Recrystallization of the crude product (1.265 g, 81.5%) from diisopropyl ether/hexane gave **5** (965 mg, 62%), m.p. 94-95^{0}C, $[\alpha]_D$ -37.6^0 (acetone); lit.[33] m.p. 97^{0}C, $[\alpha]_D$ -33.6^0 (acetone).

In another experiment D-fructose (10.06 g, 55.5 mmol) suspended in acetone (250 ml) containing iodine (745 mg, 2.94 mmol, 0.05 equiv) was stirred at room temperature for 3 h and then processed as in (a). The resultant crude product (10.20 g, 70%) was recrystallized from diisopropyl ether/hexane to give **6** (6.24 g, 43%), m.p. 117-119^{0}C, $[\alpha]_D$ -158^0 (acetone); lit.[33] m.p. 119^{0}C, $[\alpha]_D^{20}$ -161^0 (acetone).

(g) *With D-galactose.* A stirred suspension of D-galactose (1.006 g, 5.55 mmol) in acetone (50 ml) containing iodine (70.5 mg, 0.28 mmol, 0.05 equiv) was heated under reflux for 45 min and then processed as described in (a) to give essentially pure **11** (1.206 g, 83.5%) as a pure pale yellow oil, $[\alpha]_D$ -55.2^0 ($CHCl_3$); lit.[34] $[\alpha]_D^{29}$ -55^0 ($CHCl_3$).

Treatment of the pure product with *p*-toluenesulphonyl chloride and pyridine in the usual manner gave the *p*-toluenesulphonate **17** (53%) after recrystallization from ethanol, m.p. 100-102^{0}C, $[\alpha]_D$ -64.5^0 ($CHCl_3$); lit.[34] m.p. 102-103^{0}C, $[\alpha]_D$ -66^0 ($CHCl_3$).

3.4 References and notes

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SOME FURTHER ASPECTS OF THE IODINE-CATALYZED ACETALATION REACTIONS

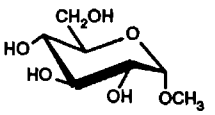
4.1 Introduction

In Chapter 3, it was demonstrated that iodine is an efficient catalyst for the isopropylidenation of sucrose, inulin and the related monosaccharides, using acetone as the solvent[1]. With sucrose and inulin efficient cleavage of the inter-glycosidic bond occurred, with concomitant isopropylidenation, to yield the respective isopropylidene acetals of the released monosaccharides. The iodine-catalyzed acetalation method could also be used for the effective synthesis of the isopropylidene acetals directly from D-glucose and D-fructose. It was, therefore, of particular interest to investigate the applicability of iodine-catalyzed acetalation reactions with carbonyl reagents other than acetone .

In this chapter three possible approaches were considered to investigate further the scope of the reaction. In section 4.2 some known benzylidene derivatives were synthesized by use of benzaldehyde dimethylacetal or benzaldehyde. Section 4.3 deals with the synthesis of the somewhat more unusual cyclohexylidene and cyclopentylidene acetals of D-glucose and D-fructose. Finally, in section 4.4 some examples of iodine-catalyzed transacetalation reactions of the known di-*O*-isopropylidene acetals of D-glucose and D-fructose are described.

4.2 Iodine-catalyzed benzylidenation reactions

Methyl α-D-glucopyranoside (**1**) is an inexpensive glycoside that can be obtained readily in nearly quantitative yields by the methanolysis of starch[2]. Methyl 4,6-*O*-benzylidene--α-D-glucopyranoside (**2**) is a well known derivative of D-glucose, and is one of the most useful and extensively studied acetal-protected intermediates in synthetic carbohydrate chemistry. It is often used as a model diol substrate, and the protecting benzylidene function at the C-4, C-6 positions can be removed quantitatively by catalytic hydrogenolysis under mild conditions. The described syntheses of **2** are based mostly on the original procedure[3] using benzaldehyde and zinc chloride, many of them requiring long reaction times. A brief history of this reaction has been described[4]. A very efficient improvement of the synthesis of **2** has been reported[5] using ultrasound, but there is always a need for new synthetic routes leading to this useful compound.



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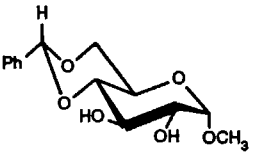


2

In order to investigate the possible iodine-catalyzed synthesis of **2**, methyl α-D-glucopyranoside (**1**) was treated with varying amounts of benzaldehyde dimethylacetal (**3**), or benzaldehyde, together with catalytic amounts of iodine. In these reactions a co-solvent was also required and 1,2-dimethoxyethane, toluene or 1,2-dichloroethane were used as such. The reaction conditions and the results obtained are collected in Table 1.

Table 1 Synthesis of methyl 4,6-O-benzylidene-α-D-glucopyranoside (2).

entry	1	equiv	reagent[a]	reaction conditions	remarks	yield	purity[d]
1	2 g	1	BADMA	16 h, dimethoxyethane		47% [b] 40% [c]	95% [b] 99% [c]
2	2 g	1	BADMA	16 h, dimethoxyethane	Dean-Stark	84% [b] 64% [c]	96% [b] 100% [c]
3	2 g	2	BADMA	6 h dimethoxyethane	Dean-Stark	quant.[b] 73% [c]	75% [b] 100% [c]
4	2 g	4	BA	17 h, dimethoxyethane	sulphite[e]	43% [b] 29% [c]	99% [b] 100% [c]
5	2 g	4	BA	3 h, toluene	Dean-Stark	quant.[b] 49% [c]	89% [b] 97% [c]
6	4 g	3	BA	8 h, dichloroethane	Dean-Stark	quant.[b] 85% [c]	100% [b] 100% [c]

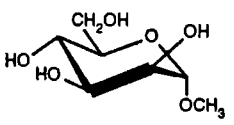
a) BADMA. Benzaldehyde dimethylactal 3, BA: benzaldehyde. b) crude product. c) after recrystallization.
d) determined by GLC. e) work-up procedure with sodium metabisulphite.

Treatment of **1** with one equivalent of benzaldehyde dimethylacetal (**3**) in boiling 1,2-dimethoxyethane for 16 h (entry 1) afforded compound **2** in only moderate yield (47%). The yield was much improved by using a simple Dean-Stark assembly (entry 2, 84%) during the reaction. This could be explained by the fact that formation of the acetal **2** is a reversible reaction whereby the selective removal of the methanol released during the reaction shifts the equilibrium in the required direction. The best results were obtained using two equivalents of **3** in boiling 1,2-dimethoxyethane for 6 h, with removal of the metanol produced (entry 3). The product was obtained in excellent yield (73%) and with good purity.

It was found that benzaldehyde itself could also be used as the benzylidenating reagent, although it seemed initially that the yields were much lower than with the dimethylacetal reagent **3**. Treatment of **1** with four equivalents of benzaldehyde in boiling 1,2-dimethoxyethane for 17 h afforded **2** in only 43% yield (entry 4). An alternative manner of processing was, therefore, examined, namely the use of aqueous sodium sulphite solution to neutralize the iodine and to remove the remaining benzaldehyde. However, several successive washings with sulphite solution were required which made this a less attractive procedure. The use of toluene and the Dean-Stark assembly (entry 5) is an efficient combination for the reaction of **1** with benzaldehyde since toluene forms an excellent azeotrope with the released water during the reaction. In this case difficulties were sometimes encountered with the isolation of **2**, because of the formation of difficult to remove minor products during the crystallization of the crude product. The most promising procedure involved the use of 1,2-dichloroethane as solvent whereby compound **2** was obtained in excellent yields without substantial impurities. The combination of 1,2-dichloroethane as the solvent using a Dean-Stark assembly gave by far the best result (entry 6): treatment of **1** with three equivalents of benzaldehyde in this manner gave **2** in almost quantitative yield. The crude product (m.p. 164-166^{0}C) was sufficiently pure (GLC) for further use as a synthetic intermediate. Recrystallization of the crude product, with only moderate loss of yield, afforded pure **2**.

From these experiments it can be concluded that iodine can be used as a suitable catalyst for the acetalation reaction of **1**. Both benzaldehyde dimethylacetal or benzaldehyde can be used as the benzylidenating reagents provided that a suitable solvent is employed.

Attention was subsequently directed to other possible iodine-catalyzed benzylidenation reactions. It was decided to investigate the synthesis of the 2,3:4,6-di-*O*-benzylidene compound **5a** from methyl α-D-mannopyranoside (**4**) and 1,2-*O*-isopropylidene-3,5-*O*-benzylidene-α-D-glucofuranose (**7**) from the monoacetal 1,2-*O*-isopropylidene-α-D-glucofuranose (**6**).



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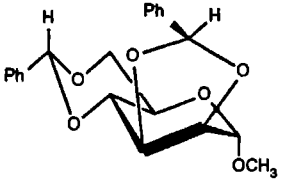
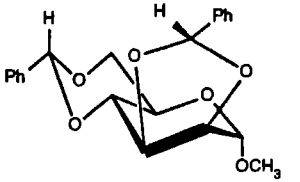
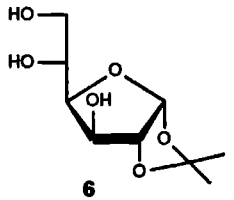


5a



5b

Methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside[9] (**5a**) is an interesting compound for the further investigation of the iodine-catalyzed benzylidenation. When methyl α-D-mannopyranoside (**4**) was treated with 2.5 equivalents of **3** in boiling 1,2-dimethoxyethane and iodine (0.05 equiv) for 24 h with the use of a Dean-Stark assembly, it afforded the *exo*-2,3-diastereomer **5a** in good yield (79%) and purity. GLC-analysis of the initial product mixture indicated the formation of a small amount (5%) of the corresponding *endo*-2,3-*O*-benzylidene compound **5b** which, however, was lost during the recrystallization of the initial product.



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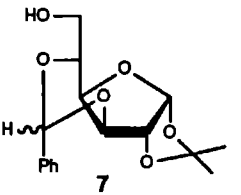

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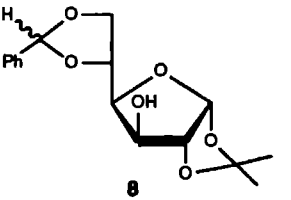


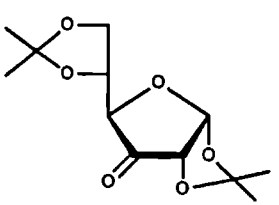
8

1,2-*O*-isopropylidene-3,5-*O*-benzylidene-α-D-glucofuranose (**7**) is a known[6,7] useful intermediate in the synthesis of 6-deoxy-α-D-glucose (D-quinovose), and is obtained from the 1,2-*O*-isopropylidene acetal **6**. The iodine-catalyzed benzylidenation of compound **6** was investigated using conditions similar to those for the synthesis of compound **2**. When the monoacetal **6** was treated with two equivalents of benzaldehyde dimethylacetal (**3**) and iodine (0.05 equiv) in boiling dichloromethane for 16 h, analysis (TLC, GLC) of the resulting product mixture indicated the formation of two main products. These were isolated by column chromatography and identified as the desired compound **7** (38%) together with a smaller amount of the alternative 5,6-*O*-benzylidene compound **8** (14%). Compound **7** could also be synthesized from the 6-*O*-*p*-nitrobenzoate[8] to minimize formation of the 5,6-*O*-benzylidene acetal **8**. It can be concluded that, under these conditions, there is a preference for benzylidenation at the 3,5-position to afford the expected six-membered acetal rather than at the 5,6-position to give a five-membered acetal.

From these experiments it can be concluded that iodine could also be used as a suitable catalyst for the benzylidenation of methyl α-D-mannopyranoside (**4**) and 1,2-*O*-isopropylidene--α-D-glucofuranose (**6**).

4.3 Synthesis of cyclohexylidene and cyclopentylidene acetals of D-glucose and D-fructose

In order to investigate further the applicability of the iodine-catalyzed acetalation procedure with other carbonyl reagents the cyclic ketones cyclohexanone and cyclopentanone were considered as possible suitable reagents for reaction with D-glucose (**9**) and D-fructose (**10**). Cyclohexylidene acetals of monosaccharides are known in carbohydrate chemistry. They tend to be more stable than the corresponding isopropylidene acetals in certain reactions. The di-*O*-cyclohexylidene acetal (**12**), for example, is often used as a substrate for oxidation to D-*ribo*-hexos-3-ulose (3-ketoglucose) (**11**) using potassium periodate in the presence of ruthenium dioxide[10,11]. Examples of cyclopentylidene acetals of D-glucose and D-fructose are rare[12,13]. This is an additional reason to investigate the iodine-catalyzed acetalation procedure with these ketones.



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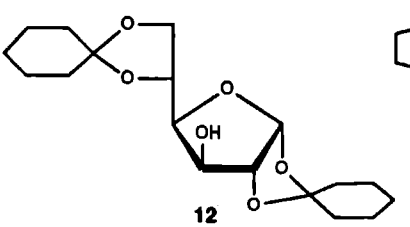

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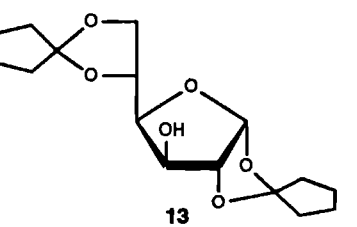

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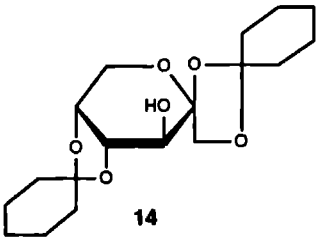

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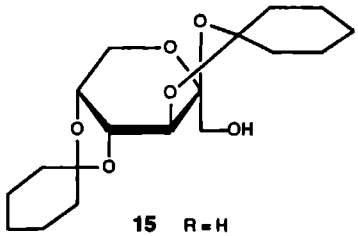
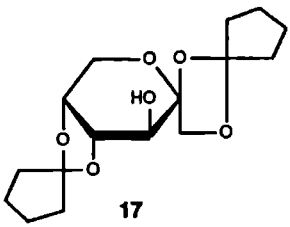


15 R = H
16 R = Ts



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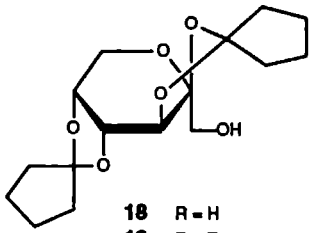


18 R = H
19 R = Ts

D-Glucose and D-fructose were treated under conditions similar to those of the iodine-catalyzed isopropylidenation method (Chapter 3). The reaction conditions and results are collected in Table 2.

Table 2 Synthesis of cyclohexylidene and cyclopentylidene acetals of D-glucose and D-fructose.

entry	reaction[a]	conditions	product	yield	purity[d]
1	glucose + CH	3 h, reflux	12	28% [b] 15% [c]	100%
2	glucose + CP	5 d, 50°C	13	1.2% [b] 1.0% [c]	100%
3	fructose + CH	16 h, RT	14	- 24% [c]	100%
4	fructose + CP	6 h 0°C + 16 h 4°C	17	29% [b] 07% [c]	100%
5	fructose + CH	45 m, reflux tosylation	15 16	29% [b]	73%
6	fructose + CP	16 h, 50°C tosylation	18 19	24% [b]	87%

a) CH = cyclohexanone, CP = cyclopentanone b) crude product. c) after recrystallization.
d) determined by GLC.

Treatment of D-glucose with boiling cyclohexanone for 3 h afforded the known[14] 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (**12**). It was found necessary to use column chromatography to remove some condensation by-products to obtain the product (28%) which could be crystallized to afford pure **12**. The reaction of D-glucose with cyclopentanone was very disappointing (entry 2) but nevertheless afforded the corresponding di-*O*-cyclopentylidene compound **13** as a pure product. In the literature very poor yields (1-2%) have also been reported[12,13] when D-glucose is treated in the traditional manner with cyclopentanone in the presence of sulfuric acid or phoshoric acid as the catalysts. It seemed probable that spiroacetal systems with 5-membered rings are not easily formed on the furanose form of glucose possibly due to ring tension[15].

The di-*O*-cyclohexylidene (**14**) and di-*O*-cyclopentylidene (**17**) derivatives of D-fructose are known[12]. They are the products of the kinetically controlled acetalation of D-fructose under conventional conditions. It was of interest to investigate whether the iodine-catalyzed reaction could provide a new route for the synthesis of these compounds, and their structural isomers. When D-fructose was treated with cyclohexanone at room temperature for 16 h (entry 3), the expected kinetic product **14** was obtained as a crystalline solid. However, treatment of D-fructose with cyclopentanone under carefully controlled conditions (entry 4) gave crystalline 1,2:4,5-di-*O*-cyclopentylidene-β-D-fructopyranoside **17** which was hitherto known[12] only as an oil, and as the corresponding tosylate. It appeared that the conditions of the iodine-catalyzed reaction are sufficiently suitable to afford compound **17** without by-products in a pure crystalline state.

It was of interest then to investigate the possibility of obtaining the hitherto unknown thermodynamically controlled compounds **15** and **18** using the procedure. D-Fructose was treated with cyclohexanone (entry 5) and cyclopentanone (entry 6) under more forcing conditions. GLC-analysis of the crude product mixtures demonstrated clearly the presence of products which were different from compounds **14** and **17**. The di-*O*-cyclohexylidene- (**15**) and di-*O*-cyclopentylidene-β-D-fructopyranose (**18**) were isolated as oils and characterized as their corresponding crystalline tosylates (**16** and **19**) which were fully substantiated by NMR spectroscopy and elemental analysis.

In the above manner some new carbohydarate derivatives were obtained using iodine as the catalyst for simple acetalation reactions. The procedure can probably be further extended, using other substrates and carbonyl reagents, and will possibly lead to a range of known, and hitherto unknown, carbohydrate acetals.

4.4 Iodine-catalyzed transacetalation reactions

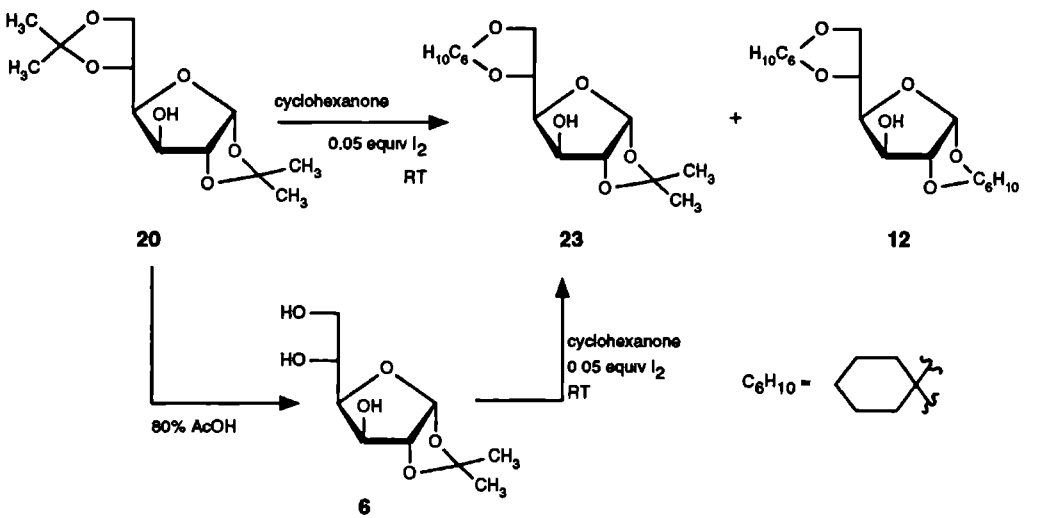
In Chapter 3 and 4 some direct iodine-catalyzed acetalation reactions are described. These acetalation reactions are characterized by very mild reaction conditions and are easy to perform. Another potential interesting field of application for the iodine-catalyzed reactions would be transacetalations. Transacetalation reactions are not common in carbohydrate chemistry and only a few examples have been described. A recent example[16] involves the use of catalytic amounts of

p-toluenesulphonic acid in dichloromethane in the presence of an excess of ethylene glycols, to remove benzylidene groups. In this way deprotection can be achieved under non-aqueous conditions.

It was considered worthwhile to investigate the use of iodine as a catalyst in transacetalation reactions. Due to the mild conditions it is possible that some interesting and selective transformations could be achieved which are difficult to realize using the conventional catalysts and methods. In this section some acetal exchange experiments are described using the di-*O*-isopropylidene acetals of D-glucose (**20**) and D-fructose (**21**) as subtrates.

Compounds **20** and **21** were treated with cyclohexanone in the presence of iodine under conditions similar to those described for the direct acetalation reactions. The crude product mixtures obtained were easily monitored by GLC-analysis. The corresponding monoacetals **6** and **22** were treated in a similar way for comparitive reasons. The reaction schemes are depicted in Scheme 1 and 2.

Scheme 1 *Transacetalation of di-O-isopropylidene-α-D-glucofuranose with cyclohexanone.*

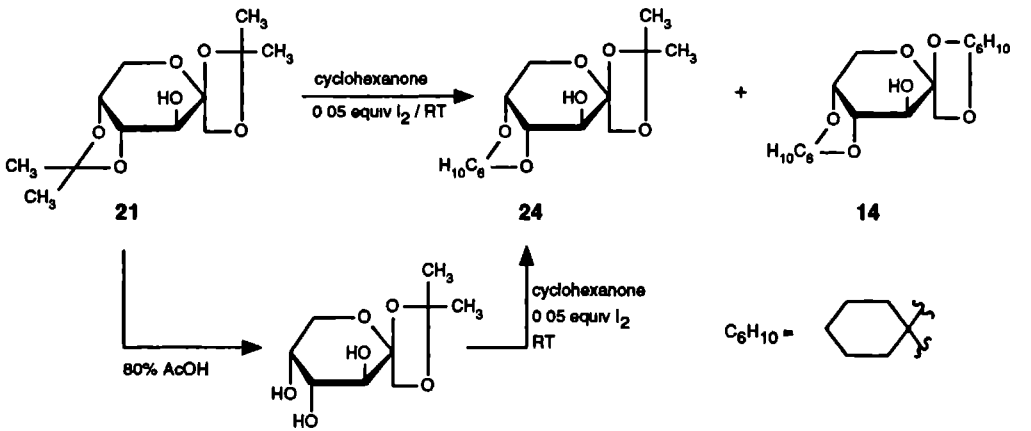


Substrate	Reagent[a]	Time	Yield	Product(s)	Purity[b]
20	CH	64 h	n.d. 58% [c]	**23** + **12** **23**	76.02 [d] 100%
4	CH	5 h	55% [c]	**23**	100%

a) CH = cyclohexanone. b) determined by GLC. c) after recrystallization. d) product ratio.

When compound **20** was treated with cyclohexanone at room temperature for 64 h, analysis (GLC) of the crude product mixture showed that the mixed acetal 1,2-*O*-isopropylidene-5,6-*O*-cyclohexylidene-α-D-glucofuranose (**23**) was the main product, together with minor amounts of the dicyclohexylidene acetal **12**. Compound **23** could be easily isolated in reasonable yield and high purity by direct crystallization. When more forcing conditions were used, *e.g.* heating for 8 h at 100°C, the di-*O*-cyclohexylidene acetal **12** was detected in larger proportions in the crude product mixture. Treatment of the monoacetal **6**, obtained from **20** by selective hydrolysis with aqueous acetic acid (80%), in the same way but for only 5 h again yielded compound **23** as the main product. It was identical (GLC and NMR) with the material obtained directly from the diacetal **20**.

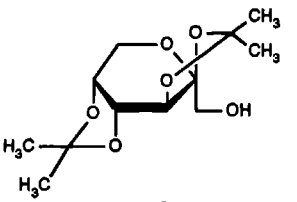
Scheme 2 *Transacetalation of di-O-isopropylidene-β-D-fructopyranose with cyclohexanone.*



Substrate	Reagent[a]	Time	Yield	Product(s)	Purity[b]
21	CH	16 h	n.d.	**24** + **14**	50 30 [f]
			19% [d]	**14**	95%
			49% [d]	**24**	94%
21	CH [c]	0 5 h	n.d.	**24** + **14**	73 16 [f]
			29% [e]		93·06 [f]
22	CH	16 h	39% [e]	**24**	99%

a) CH = cyclohexanone b) determined by GLC c) 0 01 equiv of iodine d) after column chromatography e) after recrystallization. f) product ratio

1,2:4,5-Di-*O*-isopropylidene-α-D-fructopyranose (**21**) was then treated with cyclohexanone in the presence of 0.05 equivalents of iodine at room temperature for 16 h. This experiment showed clearly (GLC) the appearance of a new compound which was identified as the mixed acetal 1,2-*O*-isopropylidene-4,5-*O*-cyclohexylidene-β-D-fructopyranose (**24**), together with the disubstituted cyclohexylidene derivative **14** (ratio 50:30). These products could be isolated in reasonable yield and purity by column chromatography. Another experiment showed that even when a very short reaction time was used (25 min), the desired mixed acetal compound **24** was obtained in reasonable yield and purity together with **14** as a minor product. The use of the 1,2-*O*-isopropylidene monoacetal of D-fructose **22**, obtained from **21** by selective hydrolysis with 80% aqueous acetic acid, also showed the formation of **24** which was identical (GLC and NMR) with the product obtained from the diacetal **21**. The same range of experiments with the 2,3:4,5-*O*-isopropylidene--β-D-fructopyranose (**25**) gave no new products and only unreacted starting material was isolated.



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From these experiments it can be concluded that under carefully controlled conditions the isopropylidene diacetals of D-glucose and D-fructose can be selectively transformed into mixed acetals using cyclohexanone in the presence of iodine as the catalyst. Substitution of the isopropylidene acetals takes place as expected at the 5,6-position of the D-glucose derivative, and at the 4,5-position of the D-fructose derivative. This was not unexpected because of the known difference in stability of these acetals. The hydrolysis with aqueous acetic acid shows this difference clearly. It is possible to use iodine-catalyzed reactions for transacetalations, which could possibly be extended to other acetals. Some interesting mixed acetals may then be otained which are difficultly accessible by the conventional, and less milder, methods.

4.5 Experimental

General methods

Optical rotations were determined with a Perkin-Elmer automatic polarimeter, model 241 MC on 1% solutions at 20°C. Thin-layer chromatography (TLC) on pre-coated plates of silica gel (Merck) was performed with dichloromethane - methanol (4/1, v/v, solvent A) or hexane - ethyl acetate (1/1, v/v, solvent B). Detection was affected by spraying with 3% H_2SO_4 in ethanol followed by heating at 140°C. GLC was performed with a Hewlett-Packard 5790 gaschromatograph; a fused silica capillary column (25m) coated with HP-1 cross-linked methyl silicone gumphase operating at

100-150^{0}C; 100^{0}C (isothermally, 5 min) followed by 5^{0}C/min for 10 min; or a temperature programme from 100-250^{0}C at 15^{0}C/min, followed by 10 min at 250^{0}C (isothermal), and nitrogen as the carrier gas (2 ml/min) was used. Compounds were identified by co-injection with authentic samples and the percentages composition of the analysed mixtures are all relative. Melting points were determined on a Reichert thermopan microscope and are uncorrected. Elemental analysis were performed on a Carlo Erba Instruments CHNS-O EA 1108 element analyzer. Mass spectra were recorded using a double focussing VG 7070E mass spectrometer using the chemical ionisation (CI) technique with methane as reaction gas. ^{1}H-NMR spectra were recorded with a Bruker AC 100 (100 MHz) or Bruker AM 400 (400 MHz) spectrometer on solutions in $CDCl_3$ (internal standard Me_4Si). ^{13}C-NMR spectra were recorded with a Bruker AC 100 or Bruker AM 400 spectrometer operating at 25 and 100.6 MHz, respectively, on solutions in $CDCl_3$ (internal Me_4Si). Pyridine was distilled from potassium hydroxide, and hexane from calcium hydride before use.

Reaction of methyl α-D-glucopyranoside (**1**) *with :*

(a) *1 equiv of 3 (entry 1).* A stirred suspension of **1** (2000 mg, 10.3 mmol) in 1,2-dimethoxyethane (75 ml) and **3** (1.55 ml, 1.0 equiv) was treated with iodine (130 mg, 0.51 mmol, 0.05 equiv) and the mixture heated under reflux for 16 h, whereon a clear solution was obtained. The cooled mixture was treated with 0.5 M aqueous sodium thiosulphate solution until colourless, concentrated *in vacuo*, and the resultant product was dissolved in dichloromethane (150 ml). The solution was washed with 10% aqueous sodium chloride solution (3 x 100 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give **2** as a colourless oil (1338 mg, 47%) which crystallized on standing. GLC-analysis: R_t 10.48 (95%). Recrystallization of the crude product (2-propanol/water, 1:3) gave pure **2** (1177 mg, 40.3%), m.p. 167-169^{0}C, $[\alpha]_D$ +101^0 ($CHCl_3$); lit.[5] m.p. 163-165^{0}C, $[\alpha]_D$ +111^0. GLC-analysis: R_t 10.57 (99%).

(b) *1 equiv of 3 and usage of a Dean-Stark assembly (entry 2).* Use of the above procedure of (a) with **1** (2.000 g, 10.3 mmol), but with the use of an Dean-Stark assembly, yielded **2** (2437 mg, 84%), GLC-analysis: R_t 10.48 (95%). Recrystallization of the crude product (2-propanol/water, 1:3) afforded pure **2** (1868 mg, 64%), GLC-analysis: R_t 10.59 (100%).

(c) *2 equiv of 3 and usage of a Dean-Stark assembly (entry 3).* Treatment of **1** (2.000 g, 10.3 mmol) as above in (a), but now with two equivalents of **3** (3.1 ml) for 6 h and with the use of an Dean-Stark assembly, gave **2** (3.2 g), GLC-analysis: R_t 10.48 (75%). Recrystallization of the crude product (2-propanol/water, 1:3) afforded pure **2** (2118 mg, 73%), GLC-analysis: R_t 10.59 (100%).

(d) *4 equiv of benzaldehyde (entry 4).* A stirred suspension of **1** (2.000 g, 10.3 mmol) in 1,2-dimethoxyethane (75 ml) and benzaldehyde (4.2 ml, 4.0 equiv) was treated with iodine (130 mg, 0.51 mmol, 0.05 equiv) and the mixture heated under reflux for 17 h, whereon a clear solution was obtained. The cooled mixture was treated with saturated aqueous sodium bisulphite solution until colourless, concentrated *in vacuo*, and the resultant product was dissolved in dichloromethane (150 ml). The solution was washed extensively with saturated aqueous sodium metabisulphite solution (9 x 100 ml) to remove the excess benzaldehyde (GLC), dried (Na_2SO_4), and concentrated *in vacuo* to

give **2** as a white solid (1234 mg, 43%). GLC-analysis: R_t 10.58 (99%). Recrystallization of the crude product (2-propanol/water, 1:3) gave pure **2** (833 mg, 29%), GLC-analysis: R_t 10.68 (100%).

(e) *4 equiv of benzaldehyde and usage of a Dean-Stark assembly (entry 5).* A stirred suspension of **1** (2.000 g, 10.3 mmol) in toluene (75 ml) and benzaldehyde (4.2 ml, 4.0 equiv) was treated with iodine (130 mg, 0.51 mmol, 0.05 equiv) and the mixture heated under reflux for 3 h, using an Dean-Stark assembly, whereon a clear solution was obtained. Processing of the reaction as described above in (a)yielded **2** (3.3 g) as a solid, GLC-analysis: R_t 10.48 (89%). Recrystallization of the crude product (2-propanol/water, 1:3) afforded pure **2** (1436 mg, 49%), GLC-analysis: R_t 10.50 (100%).

(f) *3 equiv of benzaldehyde and usage of a Dean-Stark assembly (entry 6).* A stirred suspensension of **1** (4.0 g, 20.6 mmol) in 1,2-dichloroethane (125 ml) and benzaldehyde (6.4 ml, 3.0 equiv) was treated with iodine (260 mg, 1.02 mmol, 0.05 equiv) and the mixture heated under reflux for 8 h, using an Dean-Stark assembly, whereon a clear solution was obtained. The cooled mixture was treated with 0.5 M aqueous sodium thiosulphate solution until colourless, concentrated *in vacuo*, and the resultant product was poured into a mixture of ice-water (75 ml) and hexane (75 ml) and shaken vigorously. The precipitated solid material was collected by filtration and washed with ice water (20 ml) and hexane (3 x 25 ml), air-dried to give the crude product **2** (6.0 g, 100%), m.p. 164-166^{0}C. GLC-analysis: R_t 10.50 (100%). Recrystallization of the crude product (2-propanol/water, 1:3) yielded pure **2** (4970 mg, 85%), m.p. 165-167^{0}C, $[\alpha]_D$ +109^0 ($CHCl_3$); lit.[5] m.p. 163-165^{0}C, $[\alpha]_D$ +111^0. GLC-analysis: R_t 10.60 (100%).

Methyl 2,3:4,6-di-O-benzylidene-α-D-mannopyranoside (**5a**) A stirred suspension of methyl α-D-mannopyranoside (**4**, 2000 mg, 10.30 mmol) in 1,2-dimethoxyethane (100 ml) and **3** (3.9 ml, 2.5 equiv) containing iodine (130 mg, 0.51 mmol, 0.05 equiv) was heated under reflux for 24 h using a Dean-Stark assembly, whereon a clear solution was obtained. The cooled mixture was treated with 0.5 M aqueous sodium thiosulphate solution until colourless, concentrated *in vacuo*, and the resultant product was dissolved in dichloromethane (75 ml). The solution was washed with 10% aqueous sodium chloride solution (3 x 50 ml), dried (Na_2SO_4), and concentrated *in vacuo* to afford crude **5a** as a white solid (3.7 g, 97%). Recrystallization of the material (ethanol) gave pure **5a** (2987 mg, 79%), m.p. 183^{0}C, $[\alpha]_D$ 0^0 ($CHCl_3$); lit.[9] m.p. 184^{0}C, $[\alpha]_D$ 0^0. GLC-analysis: R_t 17.87 (100%). ^{1}H-NMR ($CDCl_3$): δ 7.4 (m, 10H, phenyl), 6.29 (s, 1H, H-2,3-benzylidene), 5.64 (s, 1H, H-4,6-benzylidene), 5.64 (d, 1H, H-1), 4.62 (dd, 1H, H-3), 4.34 (t, 1H, H6a), 4.13 (d, 1H, H-2), 4.0-3.8 (m, 3H, H-4, H-5, H-6b), 3.40 (s, 3H, CH_3) ppm.

1,2-O-Isopropylidene-3,5-O-benzylidene-α-D-glucofuranose (**7**) *and 1,2-O-isopropylidene-5,6-O-benzylidene-α-D-glucofuranose* (**8**). A stirred suspension of 1,2-*O*-isopropylidene-α-D-glucofuranose **6** (1000 mg, 4.54 mmol) in dichloromethane (50 ml) and **3** (1.4 ml, 2.0 equiv) was treated with iodine (58 mg, 0.23 mmol, 0.05 equiv) and the mixture heated under reflux for 16 h using a Dean-Stark assembly, and processed as described above to give a yellow oil. Column chromatography (hexane/ethyl acetate, 6:4) of the crude product afforded **8** as a colourless oil (191

mg, 14%) which crystallized on standing. Recrystallization of the material (diisopropyl ether/hexane) gave pure **8** (151 mg, 11%), m.p. 145-147°C, $[\alpha]_D$ +22.5° ($CHCl_3$); lit.[7] m.p. 146-148°C, $[\alpha]_D$ +21.8°. GLC-analysis: R_t 9.59 (96%). ^{1}H-NMR ($CDCl_3$): δ 7.4 (m, 5H, phenyl), 5.94 (s, 1H, H-benzylidene), 5.89 (d, 1H, H-1), 4.6-4.0 (m, 6H, H-2, H-3, H-4, H-5, H-6ab), 2.74 (d, 1H, 3-OH), 1.51, 1.30 (2s, 6H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$): δ 137.50, 129.37, 128.39, 126.45 (phenyl), 111.64 (qC-isopropylidene), 105.20 (C-1), 103.96 (qC-benzylidene), 85.07, 80.97, 74.77, 73.09 (C-5, C-4, C-3, C-2)[17], 69.62 (C-6), 26.61, 26.12 (CH_3) ppm. Further elution gave compound **7** (530 mg, 38%) as a white solid. Recrystallization of the crude product (diisopropyl ether/hexane) gave pure **7** (441 mg, 32%), m.p. 148-149°C, $[\alpha]_D$ +23.8° ($CHCl_3$); lit.[7] m.p. 150°C, $[\alpha]_D$ +23.1°. GLC-analysis: R_t 9.85 (98%). ^{1}H-NMR ($CDCl_3$): δ 7.3 (m, 5H, phenyl), 6.04 (d, 1H, H-1), 5.84 (s, 1H, H-benzylidene), 4.7-3.9 (m, 6H, H-2, H-3, H-4, H-5, H-6ab), 2.08 (dd, 1H, 6-OH), 1.53, 1.33 (2s, 6H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$): δ 137.65, 129.17, 128.29, 126.20 (phenyl), 111.67 (qC-isopropylidene), 104.92 (C-1), 94.47 (qC-benzylidene), 83.63, 77.93, 74.05, 72.95 (C-5, C-4, C-3, C-2)[17], 61.92 (C-6), 26.87, 26.09 (CH_3) ppm.

1,2:5,6-Di-O-cyclohexylidene-α-D-glucofuranose (**12**). A stirred suspension of D-glucose (1.016 g, 5.64 mmol) in cyclohexanone (20 ml) was treated with iodine (70 mg, 0.28 mmol, 0.05 equiv) and the mixture heated under reflux for 3 h, whereon a clear solution was obtained. The cooled mixture was treated with 0.5 M aqueous sodium thiosulphate solution and then concentrated *in vacuo*. The resultant product mixture was dissolved in dichloromethane (50 ml) and the solution was washed with 10% aqueous sodium chloride solution (3 x 25 ml), dried (Na_2SO_4), and concentrated *in vacuo* (with addition of water to remove cyclohexanone azeotropically) to give **12** as a red-brown oil. Column chromatography (hexane/ethyl acetate, 3:1) of the crude product afforded a colourless oil (0.53 g 28%). Crystallization of the material (hexane) gave pure **12** (293 mg, 15%), m.p. 131-133°C, $[\alpha]_D$ +1.8° ($CHCl_3$); lit.[12,14] m.p. 133°C, $[\alpha]_D$ +1.6°. GLC-analysis: R_t 11.40 (100%).

1,2:5,6-Di-O-cyclopentylidene-α-D-glucofuranose (**13**). D-Glucose (5.00 g, 27.8 mmol) suspended in cyclopentanone (50 ml) containing iodine (350 mg, 1.38 mmol, 0.05 equiv) was heated at 50°C whith stirring for 5 days, and processed as described above for **12** to afford a black oil (342 mg). The by-products (UV-active) were removed by addition of hexane (100 ml), treatment with active charcoal, boiling, and filtration of the mixture. The filtrate was concentrated *in vacuo* to give an oil which was subjected to column chromatography (hexane/ethyl acetate, 3:1) to afford the crude product **13** as yellow crystals (100 mg, 1.2%). Recrystallization of the material (hexane) gave pure **13** (85 mg, 1%), m.p. 104°C, $[\alpha]_D$ +8.4° ($CHCl_3$); lit.[12,14] m.p. 104°C, m.p.[13] 106-107°C, $[\alpha]_D$ +8.9°. GLC-analysis: R_t 10.60 (100%).

1,2:4,5-Di-O-cyclohexylidene-β-D-fructopyranose (**14**). D-Fructose (5.00 g, 27.8 mmol) suspended in cyclohexanone (50 ml) containing iodine (350 mg, 1.38 mmol, 0.05 equiv) was stirred at room temperature for 16 h, and processed as described above for **12** to afford a dark purple oil (342 mg). The by-products (UV-active) were removed by treatment with active charcoal in boiling hexane (50

ml), followed by filtration, and cooling of the filtrate whereon pure **14** crystallized (2306 mg, 24%), m.p. 145-146^{0}C, $[\alpha]_D$ -122^0 (acetone); lit.[11,12] m.p. 146^{0}C, $[\alpha]_D$ -123^0. GLC-analysis: R_t 11.10 (100%).

2,3:4,5-Di-O-cyclohexylidene-β-D-fructopyranose (**15**). D-Fructose (5.00 g, 27.8 mmol) suspended in cyclohexanone (50 ml) containing iodine (350 mg, 1.38 mmol, 0.05 equiv) was heated under reflux whith stirring for 45 min, and then processed as described above for **12** to afford a dark oil. Column chromatography (hexane/ethyl acetate, 4:1) of the crude product afforded **15** as an orange oil (3.97 g, 42%). Treatment of the material with active charcoal in boiling hexane (50 ml), followed by filtration, and cooling of the filtrate did not afford crystalline material. The filtrate was concentrated *in vacuo* to afford **15** as an orange oil (2.70 g, 29%). GLC-analysis: R_t 12.50 (73%).

2,3:4,5-Di-O-cyclohexylidene-β-D-fructopyranoside 1-p-toluenesulphonate (**16**). Treatment of the crude product **15** (2.70 g, 7.90 mmol) in the usual manner with pyridine (5 ml) and *p*-toluenesulphonyl chloride (3.0 g) afforded the *p*-toluenesulphonate **16** (1.87 g, 48%) after recrystallization from ethanol, m.p. 101-102^{0}C, $[\alpha]_D$ -33.5^0 ($CHCl_3$). Calculated for $C_{25}H_{34}SO_8$ (494.59): C 60.71%, H 6.93%, S 6.48%; Found: C 60.50%, H 6.85%, S 6.32%. ^{1}H-NMR ($CDCl_3$): δ 7.79, 7.34 (2d, 4H, phenyl), 4.58 (dd, 1H, $J_{4,5}$ 7.8 Hz, H-4), 4.31 (d, 1H, $J_{3,4}$ 2.6 Hz, H-3), 4.19 (dd, 1H, H-5), 4.02 (dd, 2H, H-1a+b), 3.87 (dd, 1H, $J_{6a,6b}$ 12.9 Hz, H-6a), 3.70 (d, 1H, H-6b), 2.44 (s, 3H, CH_3), 1.70-1.37 (m, 20H, CH_2) ppm.

1,2:4,5-Di-O-cyclopentylidene-β-D-fructopyranose (**17**). D-Fructose (5.00 g, 27.8 mmol) suspended in cyclopentanone (50 ml) containing iodine (350 mg, 1.38 mmol, 0.05 equiv) was stirred at 0^{0}C for 6 h, and then processed as described above for **12** to afford the crude crystalline product **17** (2.48 g, 29%). Recrystallization of the crude product (hexane) gave pure **17** (582 mg, 7%), m.p. 116^{0}C, $[\alpha]_D$ -126.6^0 ($CHCl_3$). GLC-analysis: R_t 10.60 (100%). Calculated for $C_{16}H_{24}O_6$ (312.35): C 61.52%, H 7.74%; Found: C 61.48%, H 7.64%. CI-MS: *m/z* 313 (M^+ + 1). ^{1}H-NMR ($CDCl_3$): δ 4.16 (d, 1H, $J_{1b,1a}$ 8.8 Hz, H-1b), 4.11-4.06 (m, 3H, H-4, H-5, H-6a), 4.04 (d, 1H, $J_{6b,6a}$ 12.8 Hz, H-6b), 3.89 (d, 1H, H-1a), 3.63 (dd, 1H, $J_{3,4}$ 6.2 Hz, H-3), 2.06 (d, 1H, $J_{OH,3}$, OH), 2.00-1.64 (m, 16H, CH_2) ppm.

2,3:4,5-Di-O-cyclopentylidene-β-D-fructopyranose (**18**). D-Fructose (5.00 g, 27.8 mmol) suspended in cyclopentanone (50 ml) containing iodine (350 mg, 1.38 mmol, 0.05 equiv) was heated at 45^{0}C with stirring for 16 h, and processed as described above for **12** to afford an orange oil (2.10 g, 24%). GLC-analysis: R_t 10.60 (87%).

2,3:4,5-Di-O-cyclopentylidene-β-D-fructopyranoside 1-p-toluenesulphonate (**19**). Treatment of the crude product **18** (2.098 g, 6.70 mmol) in the usual manner with pyridine (5 ml) and *p*-toluenesulphonyl chloride (2.5 g) afforded the *p*-toluenesulphonate **19** (1.46 g, 37%) after recrystallization from ethanol, m.p. 114^{0}C, $[\alpha]_D$ -22.6^0 (acetone). Calculated for $C_{23}H_{30}SO_8$ (466.55): C 58.21%, H 6.48%, S 6.87%; Found: C 58.92%, H 6.37%, S 5.71%. ^{1}H-NMR ($CDCl_3$): δ 7.79, 7.34 (2d, 4H, phenyl), 4.46 (dd, 1H, $J_{4,5}$ 8.0 Hz, H-4), 4.20 (d, 1H, $J_{3,4}$ 2.5 Hz, H-3), 4.10 (d, 1H, H-5), 4.01 (dd, 2H, H-1a+b), 3.84 (dd, 1H, $J_{6a,6b}$ 13.0 Hz, H-6a), 3.69 (d, 1H, H-6b), 2.44 (s, 3H, CH_3), 2.02-1.64 (m, 16H, CH_2) ppm.

1,2-O-Isopropylidene-5,6-O-cyclohexylidene-α-D-glucofuranose (**23**). A suspension of 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (**20**, 1.000 mg, 3.84 mmol) in cyclohexanone (50 ml) was treated with iodine (50 mg, 0.20 mmol, 0.05 equiv) and the mixture stirred at room temperature for 64 h, whereon a clear solution was obtained. The cooled mixture was treated with 0.5 M aqueous sodium thiosulphate solution, concentrated *in vacuo*, and the resultant product was dissolved in dichloromethane (50 ml). The solution was washed with 10% aqueous sodium chloride solution (3 x 25 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give a yellow oil. The crude oil was further concentrated *in vacuo* (1.5 mm Hg) to completely remove cyclohexanone to afford the crude product as a light yellow oil which crystallized on standing. GLC-analysis: R_t 7.37 (**23**, 76%), 10.04 (**12**, 2%). Recrystallization of the crude product (hexane) gave pure **23** (666 mg, 58%), m.p. 114-115°C, $[\alpha]_D$ -8.4° ($CHCl_3$). GLC-analysis: R_t 7.41 (100%). Calculated for $C_{15}H_{24}O_6$ (300.34): C 59.99%, H 8.05%; Found: C 60.10%, H 7.97%. ^{1}H-NMR ($CDCl_3$): δ 5.94 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.52 (d, 1H, H-2), 4.33 (m, 1H, H-5), 4.31 (d, 1H, H-3), 4.15 (dd, 1H, H-6b), 4.06 (dd, 1H, H-4), 3.98 (dd, 1H, $J_{6a,6b}$ 13.8 Hz, H-6a), 2.94 (bs, 1H, 3-OH), 1.7-1.5 (m, 10H, CH_2), 1.49, 1.32 (2s, 6H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$, DEPT-135): δ 111.72, 110.22 (q-C acetal), 105.23 (C-1), 84.97, 81.24, 75.11, 73.04 (C-5, C-4, C-3, C-2)[17], 67.26 (C-6), 37.39, 34.56, 24.97, 24.08, 23.71 ($\underline{C}H_2$ hexylidene), 26.78, 26.11 (CH_3) ppm.

In another experiment, 1,2-*O*-isopropylidene-α-D-glucofuranose (**6**, 500 mg, 2.27 mmol) suspended in cyclohexanone (25 ml) containing iodine (30 mg, 0.12 mmol, 0.05 equiv) was stirred at room temperature for 5 h, and processed as described above to afford **23** as a white solid. GLC-analysis: R_t 7.37 (**23**, 94%), 10.04 (**12**, 1%). Recrystallization of the crude product (hexane) gave pure **23** (364 mg, 55%), m.p. 113-114°C, $[\alpha]_D$ -8.7° ($CHCl_3$). GLC-analysis: R_t 7.97 (100%).

1,2-O-Isopropylidene-4,5-O-cyclohexylidene-β-D-fructopyranose (**24**). 1,2;4,5-di-*O*-isopropylidene-β-D-fructopyranose (**21**, 1.000 mg, 3.84 mmol) suspended in cyclohexanone (50 ml) containing iodine (50 mg, 0.14 mmol, 0.05 equiv) was stirred at room temperature for 16 h, and processed as described above to afford a yellow oil. GLC-analysis: R_t 7.83 (**24**, 50%), 9.88 (**14**, 30%). Column chromatography (hexane, ethyl acetate, 3:1) of the crude product afforded compound **14** (251 mg, 19%) as a white solid, m.p. 130-132°C, $[\alpha]_D$ +2° ($CHCl_3$). GLC-analysis: R_t 9.72 (100%). Further elution gave compound **24** (534 mg, 49%) as a white solid, m.p. 98-100°C, $[\alpha]_D$ -128° ($CHCl_3$). GLC-analysis: R_t 9.72 (100%).

In another experiment, compound **21** (1.000 mg, 3.84 mmol) suspended in cyclohexanone (15 ml) containing iodine (10 mg, 0.04 mmol, 0.01 equiv) was stirred at room temperature for 0.5 h, and processed as described above to afford a yellow oil. GLC-analysis: R_t 8.27 (**24**, 73%), 11.12 (**14**, 16%). Recrystallization of the crude product (hexane) gave pure **24** (334 mg, 29%) as white crystals, m.p. 100-101°C, $[\alpha]_D$ -128.2° ($CHCl_3$). GLC-analysis: R_t 8.28 (93%).

In another experiment, 1,2-*O*-isopropylidene-β-D-fructopyranose (**22**, 500 mg, 2.27 mmol) suspended in cyclohexanone (25 ml) containing iodine (30 mg, 0.12 mmol, 0.05 equiv) was stirred at room temperature for 16 h, and processed as described above to afford crude **24** as a white solid. Recrystallization of the crude product (hexane) gave pure **24** (334 mg, 29%) as white crystals, m.p.

100-101^{0}C, $[\alpha]_D$ -127.6^0 ($CHCl_3$). GLC-analysis: R_t 8.27 (99%). Calculated for $C_{15}H_{24}O_6$ (300.34): C 59.99%, H 8.05%; Found: C 60.09%, H 8.07%. ^{1}H-NMR ($CDCl_3$): δ 4.19 (d, 1H, H-1a), 4.16 (d, 1H, H-4), 4.13 (dd, 1H, H-6a), 4.09 (d, 1H, H-6b), 4.00 (t, 1H, H-5), 3.97 (d, 1H, $J_{1b,1a}$ 8.8 Hz, H-1b), 3.65 (d, 1H, $J_{3,4}$ 7.0 Hz, H-3), 2.30 (bs, 1H, 3-OH), 1.7-1.4 (m, 10H, CH_2), 1.51, 1.44 (2s, 6H, CH_3) ppm. ^{13}C-NMR (DEPT-135, $CDCl_3$): δ 111.74, 109.92 (q-C acetal), 104.50 (C-2), 77.32, 72.87, 70.60 (C-4, C-5, C-3)[17], 72.19 (C-1), 60.73 (C-6), 37.65, 35.12, 24.79, 23.93, 23.73 ($\underline{C}H_2$ hexylidene), 26.32, 26.22 (CH_3) ppm.

4.6 References and notes

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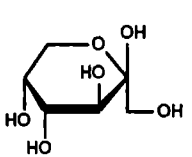
IODINE-CATALYZED GLYCOSIDATION REACTIONS OF SUCROSE, D-GLUCOSE, D-FRUCTOSE AND RELATED COMPOUNDS

5.1 Introduction

After D-glucose, D-fructose (**1**) is the second most abundant monosaccharide occurring in nature. It is found in the free state in vegetables, fruit and honey, and also as a constituent unit of di, tri and oligosaccharides such as sucrose (**2**), raffinose and inulin (**3**)[1,2] (see Chapter 1 and 3).



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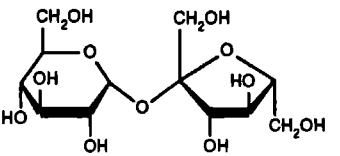

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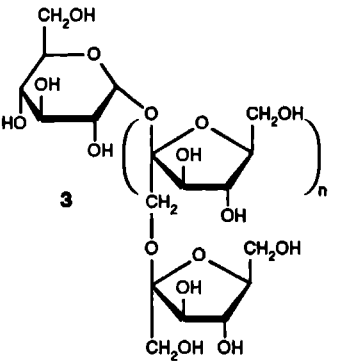
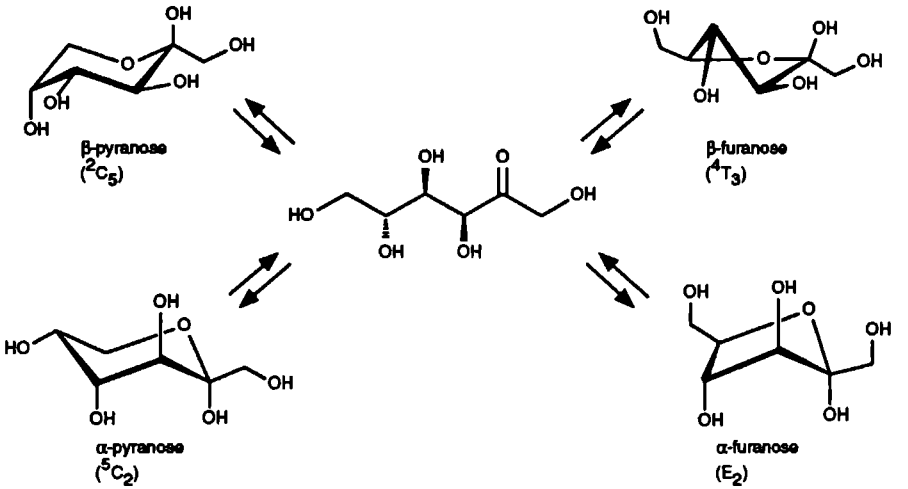


3

Currently, there is an increasing interest in the synthesis of useful new products based on D-fructose, *e.g.* non-ionic surfactants. D-Fructose is becoming more easily available, *e.g.* via the high fructose corn syrups (HFCS). High fructose corn syrup is produced commercially from starch, which contains D-glucose, using a two step enzymatic process[3,4]. In the first step starch is hydrolysed to D-glucose using the bio-catalysts α-amylase and glucoamylase. Isomerisation of D-glucose using immobilised glucose-isomerase yields a mixture of D-fructose and D-glucose, containing *ca* 55% D-fructose. With the use of Ca^{2+} ion-exchange resins the percentage of D-fructose in the mixture can be increased to 90%. HFCS is as sweet as invert sugar, the 50-50% mixture of D-glucose and D-fructose obtained by the acid or enzymatic hydrolysis of sucrose. Inulin is also becoming of interest as a new major source of D-fructose, either after enzymatic hydrolysis, or directly[5].

Previously it was difficult to obtain D-fructose in a crystalline form, and only the β-D-fructopyranose tautomer was obtained crystalline. D-Fructose, unlike the aldoses and the other ketohexoses, exhibits a complex mutarotational behaviour in solution leading to mixtures that contain all of the five possible tautomers (Scheme 1). The tautomeric ratio depends on the solvent, the time, temperature and concentration and has been studied using ^{1}H-NMR spectroscopy[6].

Scheme 1 *Tautomeric forms of D-fructose in their preferred (β-p, α-p) and most probable (β-f and α-f) conformations.*



In contrast to D-glucose, the chemistry of D-fructose has developed at a much slower rate, partly caused by the complex equilibrium behaviour and generally by the difficulties encountered in obtaining fructose derivatives in a pure crystalline state.

5.2 Iodine-catalyzed glycosidation reaction of D-fructose, inulin and sucrose

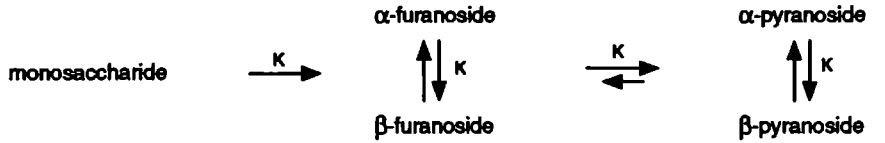
5.2.1 *Introduction*

There is currently an increasing interest in long-chain alkyl D-glycosides for use as amphiphiles in soaps and cosmetic products. In a recent Japanese patent[7] decyl D-fructofuranosides, which are mild to the skin and have good foaming properties, have been suggested as components for shampoos, face cleansers and lotions.

One of the simplest methods for the synthesis of glycosides is the well known Fischer glycosidation procedure in which an aldose or a ketose is treated with alcohols containing an acid catalyst, *e.g.* hydrogen chloride, a sulfonic acid or a strong acid ion-exchange resin. In general, glycoside synthesis is a complex process due to a number of distinguishable competing reactions leading, at equilibrium, to anomeric mixtures of furanosides and pyranosides[8].

The use of ferric chloride as catalyst has been investigated recently and led to an efficient synthesis of the methyl D-glycofuranosides of D-glucose and D-galactose[9].

Scheme 2



In the early stages of the glycosidation reaction glycofuranosides can be isolated as kinetic products, and are formed at a relatively high rate (Scheme 2), before their subsequent conversion, at a much lower rate, into the thermodynamically more stable glycopyranosides[10]. For these reasons the reaction is often performed at moderate temperature for short periods of time, monitored by following changes in optical rotation, or by chromatography, and terminated at the maximum concentration of the furanosides. The Fischer glycosidation procedure performed in this manner is one of the few direct methods used to obtain furanosides specifically.

The normal Fischer glycosidation reaction of D-fructose (**1**), catalyzed by mineral acids or other acid catalysts, including ion-exchange resins, results in a complex equilibrium mixture of the furanosides (α + β) and pyranosides (α + β), which require separation by column chromatography[11,12]. Unlike the aldosides there is little difference in the acid stability of D-fructofuranosides and D-fructopyranosides, so overall control of eventual ring-size during the reaction is difficult[13]. Few glycosides of D-fructose are known, especially D-fructofuranosides, possibly due to the slight differences in the stability of the two anomeric forms.

Until recently the benzyl β-D-fructopyranoside (**38**) and the 2'-chloroethyl β-D-fructopyranoside (**39**) were the only two crystalline glycosides of D-fructose obtainable directly without the use of chromatography[13,14]. A more recent[15] study has extended the range considerably. The crystalline ω-halogenoalkyl derivatives **39 - 42** were isolated in good to moderate yields by direct treatment of D-fructose (**1**), sucrose (**2**) or inulin (**3**) with the corresponding ω-halogenoalkyl alcohols. Similar treatment of **1** with allyl alcohol containing *ca* 1% hydrogen chloride yielded[16] the allyl glycoside **43** (43%). Catalytic hydrogenolysis of these derivatives provided an essentially direct route to the known[12] corresponding short-chain alkyl β-D-fructosides (**14-24-30**) without resource to column chromatography. Some simple alkyl β-D-fructopyranosides have been claimed to have potentially interesting medicinal and biological properties, including the suppression of IgE antibody formation[12,17].

The methanolysis of D-fructose and L-sorbose has been studied in some detail using ^{14}C-labelled substrates[18]. These experiments confirmed that for these ketoses, in concurrence with analogous reactions of aldoses, the furanosides are the main initial products and that these then isomerise substantially to pyranosides. For fructose however, half of the glycosides remain at equilibrium in their five-membered ring forms probably due to their similar acid stability constants[13]. Typically methanolysis of D-fructose in the presence of 0.1% hydrogen chloride gave a final mixture of the α-pyranoside, β-pyranoside, α-furanoside, and β-furanoside (ratio 3:46:25:26).

When the reactions were repeated under essentially kinetic conditions (methanolic 0.001% hydrogen chloride), the furanosides were clearly the main products. The acyclic dimethyl acetal **45**, proposed initially by Fischer[19] as a possible glycoside precursor, could not be detected in the reaction mixture. It was found that the furanosides are the initial products but, as with some aldoses, they are not initially formed in their equilibration ratio.

In general the glycosidation of D-fructose is very sensitive to the actual reaction conditions. An auto-transformation[20] of fructose in ethanol without using any catalyst has been described. Eight different products were formed by dimerization, isomerization and degradation processes. A substantial amount of ethyl β-D-fructopyranoside (**14**) was also produced. The methanolysis of D-fructose catalyzed by cation exchange resins has also been studied in some detail. In this study it was claimed that the β-furanoside, formed initially, then anomerizes to an equilibrium mixture of α- and β-D-furanosides[21].

It has been demonstrated[22] that various carbohydrate acetals and dithioacetals can be cleaved by dilute solutions of iodine in methanol. The product mixtures were composed mainly of methyl glycofuranosides, approximating in composition to the early stages of conventional acid catalyzed glycosidation reaction. The methyl β-D-glycofuranosides were preponderant. Benzylidene, ethylidene and isopropylidene acetals were cleaved at room temperature, or by heating under reflux for short periods. Certain derivatives having a free hydroxyl group at the anomeric center were converted into methyl glycosides if the reaction mixture was heated under reflux for prolonged periods. Treatment of the isopropylidene acetals of D-fructose afforded methyl β-D-fructofuranoside (**6**) and methyl α-D-fructofuranoside (**4**) as the main products in a ratio of 9:1. It was also claimed that simple glycosides and disaccharides did not undergo cleavage of their glycosidic linkage under the conditions employed.

It has been demonstrated recently (Chapter 3) that iodine is also a very mild, and useful catalyst for the isopropylidenation of sucrose, inulin and their related monosaccharide units D-fructose (**1**) and D-glucose (**44**). Very efficient cleavage of the inter-glycosidic bond, with concomitant isopropylidenation, occurred to yield diacetals of the released monosaccharides[23]. The reaction conditions are particularly mild and selective, and iodine was used in very low catalytic amounts (0.05 mol%). The described acetalation method could be used also for an efficient synthesis of the isopropylidene acetals of monosaccharides, such as D-glucose, D-fructose and D-galactose.

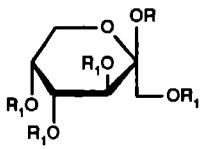
The direct glycosidation of D-fructose with alcohols catalyzed by iodine was therefore investigated subsequently as a possible method for the formation of alkyl D-fructofuranosides and the results are reported in this Chapter. Szarek *et al*[22] had not noted previously the direct reaction of free sugars with alcohols in this manner. Iodine turned out to be a very useful catalyst in some direct glycosidation reactions. It was demonstated that the glycosidation procedure led to the efficient formation of D-fructofuranosides as the main products. The method proceded in high yields and was simple to perform and process. In general a much greater control of product ratios was possible compared with the standard Fischer-type procedure.

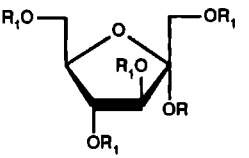
The iodine-catalyzed cleavage-glycosidation of sucrose (**2**) and inulin (**3**) to yield mixtures of alkyl D-glycofuranosides as the main products was also subsequently investigated.

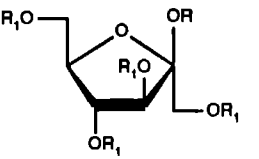
Various aspects of these reactions are described in this chapter.

5.2.2 *Results and Discussion*

Chart 1



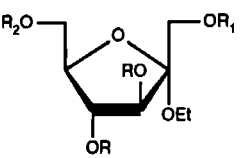




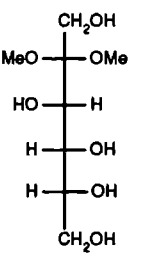
1 R = H, R_1 = H
8 R = Me, R_1 = H
9 R = Me, R_1 = Ac
14 R = Et, R_1 = H
15 R = Et, R_1 = Ac
24 R = Pr, R_1 = H
25 R = Pr, R_1 = Ac
30 R = Bu, R_1 = H
31 R = Bu, R_1 = Ac
36 R = Oc, R_1 = H
37 R = Oc, R_1 = Ac
38 R = $CH_2C_6H_5$, R_1 = H
39 R = CH_2CH_2Cl, R_1 = H
40 R = CH_2CH_2Br, R_1 = H
41 R = $CH_2CH_2CH_2Cl$, R_1 = H
42 R = $CH_2CH_2CH_2CH_2Cl$, R_1 = H
43 R = $CH_2CH{=}CH_2$, R_1 = H

4 R = Me, R_1 = H
5 R = Me, R_1 = Ac
10 R = Et, R_1 = H
11 R = Et, R_1 = Ac
20 R = Pr, R_1 = H
21 R = Pr, R_1 = Ac
26 R = Bu, R_1 = H
27 R = Bu, R_1 = Ac
32 R = Oc, R_1 = H
33 R = Oc, R_1 = Ac

6 R = Me, R_1 = H
7 R = Me, R_1 = Ac
12 R = Et, R_1 = H
13 R = Et, R_1 = Ac
22 R = Pr, R_1 = H
23 R = Pr, R_1 = Ac
28 R = Bu, R_1 = H
29 R = Bu, R_1 = Ac
34 R = Oc, R_1 = H
35 R = Oc, R_1 = Ac



16 R_1 = R_2 = Trt, R = H
17 R_1 = R_2 = Trt, R = Ac
18 R = R_1 = H, R_2 = Trt
19 R = R_1 = Ac, R_2 = Trt



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When D-fructose (**1**) was treated with a catalytic amount of iodine (0.05 equiv) in boiling methanol for 2 h, analysis (TLC, solvent A) indicated three products with mobilities expected for glycosides. There appeared to be no traces of unreacted compound **1** in the mixtures. The isolated product mixture was acetylated in the usual manner (acetic anhydride - pyridine). GLC-analysis of the acetylated mixture revealed the presence of three individual components which were identified as the peracetates of methyl α-D-fructofuranoside (**5**, 47%), methyl β-D-fructofuranoside (**7**, 43%) and methyl β-D-fructopyranoside (**9**, 10%) (Chart 1). The result demonstrated that the fructofuranosides are the major products in this glycosidation reaction and that the β-D-fructopyranoside is formed only as minor product. When D-fructose (**1**) was equilibrated in boiling methanol for 30 min, before addition of catalytic iodine, after acetylation the resulting

product mixture was shown to contain the peracetates **5**, **7** and **9** in essentially the same ratio (50:41:9). Identification of these products was also accomplished using ^{13}C-NMR spectroscopy. The anomeric C-2 atoms of the fructosides have characteristic and well defined values[24] in their NMR-spectra.

The results were comparable with those obtained by the iodine-catalyzed acetal deprotection method of Szarek *et al*[22] where a product mixture containing 90% of furanosides was also obtained. However, in the present study of direct glycosidation of D-fructose much lower quantities of iodine were used, *e.g.* 0.05 molar equivalent in place of the 0.35 equivalent (1% w/v) used in the acetal deprotection procedure . It is apparent that quite low catalytic amounts of iodine are sufficient to obtain complete glycosidation of D-fructose thereby avoiding possible side-reactions. Possible by-products from the glycosidation reaction of D-fructose, such as 2,6-anhydro-β-D-fructofuranose and various D-fructose di-anhydrides, were not observed in this study[25,26]. These side-products are obtained under much more forcing conditions, *e.g.* thermolysis of sucrose in the presence of alcohols and dimethyl sulfoxide[25] or treatment of D-fructose with methanol in the presence of hydrogen fluoride or sulfuric acid[26]. Another noteworthy difference is that in the acetal deprotection procedure[22] a clear preference for the formation of the methyl β-D-furanoside over its α-D-anomer was observed using the isopropylidene derivatives of D-fructose. In the present study the β-furanoside and α-furanoside anomer are formed in almost equal amounts. The formation of both furanosides in approximately equal amounts has been observed previously in the methanolysis of D-fructose in the presence of cation exchange resins[21].

The crude reaction product from the glycosidation reaction of fructose with methanol could be purified directly using column chromatography. In this manner pure methyl α-D-fructofuranoside **4** (29%) was obtained, together with a mixture of methyl β-D-fructofuranoside **6** and methyl β-D-fructopyranoside **8** (61%). Acetylation of the methyl α-D-furanoside **4** afforded the corresponding pure acetate **5** and acetylation of the mixture of **6** and **8** gave the corresponding acetates **7** and **9**. In a previous study[21] the α-furanoside was isolated by selective enzymatic hydrolysis of the β-anomer in the anomeric mixture. The relatively high yield of the α-D-fructofuranoside merits further comment. It had been demonstrated[27,28] that a 1,2-*cis*-OH/OMe interaction in methanol is more destabilizing than the analogous OH/OH interaction in water. However, the OH/CH_2OH interaction of the α-anomer, considered to be the most unfavoured interaction in a furanoid ring, equals the OH/OMe interaction of the β-anomer. From these arguments it can be deduced that both fructofuranoside anomers can be formed in equal amounts. These results are in agreement with those of Bethell and Ferrier[28] from investigations on the acid catalyzed methanolysis of isotopically labelled D-fructose.

Inulin (**3**) proved to be another suitable substrate for the iodine-catalyzed glycosidation reaction. This fructofuranosyl- containing oligosaccharide was treated with a catalytic amount of iodine (0.05 equiv) in boiling methanol for 3 h and, after the standard acetylation procedure the crude product mixture was shown to contain the methyl D-fructosides **5**, **7** and **9**. The furanosides were again clearly the main products (90%), comparable with the results obtained by using

D-fructose as the substate for the glycosidation reaction. In this reaction inulin is therefore a good direct source of D-fructose as substate. There is increasing interest in the application of inulin as an alternative source of useful carbohydrate derivatives[5].

The scope of the simple iodine-catalyzed glycosidation reaction was then investigated further in the presence of other alcohols. Treatment of D-fructose (**1**) with a catalytic amount of iodine (0.05 equiv) in boiling ethanol for 2 h afforded a clear solution which contained three main products (TLC, solvent A). The isolated crude material was acetylated in the standard manner, and after GLC-analysis, the product mixture was found to consist of the peracetates of ethyl α-D-fructofuranoside (**11**, 36%), ethyl β-D-fructofuranoside (**13**, 28%) and ethyl β-D-fructopyranoside (**15**, 35%). The furanosides were again the main products but in contrast to the reaction with methanol the amount of the β-pyranoside isomer was increased possibly due to the higher temperature of the reaction at equilibrium. When the reaction of **1** in ethanol was conducted at *ca* 65^0 C, rather than at the boiling point of ethanol (78^0 C), the resulting product mixture was shown to contain *ca* 90% of the peracetates ethyl D-fructofuranosides **11** and **13** in a ratio of 57:37. These results indicate that the iodine-catalyzed glycosidation procedure of D-fructose is possibly related to the temperature of the reaction. The crude product of the reaction, without subsequent acetylation, was purified directly by column chromatography to afford pure ethyl α-D-fructofuranoside **10** (33%) and a mixture of the ethyl β-D-fructofuranoside **12** and ethyl β-D-fructopyranoside **14** (42%). From the latter mixture pure compound **14** was obtained by crystallization. Acetylation of the α-furanoside **10** afforded the corresponding pure acetate **11**.

The glycosidation reaction of D-fructose with ethanol could also be performed at room temperature, but much longer reaction times (7 days) were required. Following the same methodology the ethyl α-D-furanoside **10** was isolated (30%) from the crude product together with a mixture of the β-furanoside **12** and β-pyranoside **14** (40%). Acetylation of the latter mixture afforded the corresponding acetates **13** and **15** (85:15). As expected the furanosides are clearly the main products under these kinetically controlled conditions. The ethyl β-D-pyranoside peracetate **15** was identical with the corresponding peracetate of authentic ethyl β-D-fructopyranoside, prepared by an alternative method[15]. This was also established by comparison of the ^{1}H and ^{13}C-NMR spectra.

The reaction of sucrose in ethanol has been described using copper chromium oxide as a catalyst[29]. Ethyl fructofuranosides isolated from the reaction mixture were characterized as their trityl derivatives. Tritylation of the ethyl α-D-fructofuranoside **10** as described above afforded the known di-trityl α-D-fructofuranoside **16**[29], and the hitherto unknown mono-trityl α-D-fructofuranoside **18**, in which the trityl group is situated at the C-6 position of the fructofuranoside ring. Both compounds were characterized as their corresponding crystalline peracetates **17** and **19**, the di-trityl α-D-fructofuranoside **17** was shown to crystallize as an ethanolate.

The iodine-catalyzed glycosidation reaction of inulin (**3**) with ethanol was also possible but required somewhat longer reaction times (4 h), and the use of column chromatography to remove some minor impurities from the crude product. Acetylation of the material containing the fructofuranosides yielded the corresponding peracetates **11**, **13** and **15**, in which the ethyl

fructofuranosides were the main products (75%).

The reaction conditions for the glycosidation reaction of D-fructose with 1-propanol also needed to be modified slightly compared to the reactions with methanol and ethanol. Moderated reaction conditions were used (6 h 60°C) to avoid possible side-reactions in boiling 1-propanol. Column chromatography of the crude product mixture yielded pure propyl α-D-fructofuranoside **20** (22%) and a mixture of the propyl β-D-fructofuranoside **22** and propyl α-D-fructopyranoside **24** (41%). Acetylation of the propyl α-D-fructofuranoside **20** afforded the pure corresponding acetate **21**, and acetylation of the mixture of compounds **22** and **24** gave the corresponding acetates **23** and **25**. The propyl β-D-fructopyranoside tetra-acetate **25** was identical with that of an authentic sample prepared by another method[15]. Further analysis of this mixture of **21**, **23** and **25** showed that the content of furanosides was approximately 70%.

The reaction of D-fructose with 1-butanol gave very poor results. The butyl fructosides were formed but a considerable amount of unreacted D-fructose was also detected (TLC). The solubility of D-fructose decreases significantly in going from methanol to 1-butanol and at the same time increasing reaction temperatures can give rise to unwanted side-reactions such as degradation. Additional problems involve the possible formation of 5-(hydroxymethyl)-2-furaldehyde and the formation of anhydrides of D-fructose at elevated temperatures (*vide supra*). This problem was solved by the development of a two-step reaction - one-pot procedure. In the first step the mixture of methyl fructosides from D-fructose were formed by the glycosidation procedure described above. In the second step these products were then subsequently transformed by a transglycosidation reaction into the required corresponding butyl fructosides, using iodine as the catalyst. In this manner, using ambient temperature in the second step, the butyl fructosides could be obtained in moderate yield (40%). Column chromatography of the crude product mixture afforded pure butyl α-D-fructofuranoside **26** (20%), and a mixture of the butyl β-D-fructofuranoside **28** and butyl β-D-fructopyranoside **30**, from which pure **30** could be obtained by selective crystallization. Compound **30** and some other simple alkyl β-D-fructopyranosides, as already mentioned before (section 5.2.1), have been claimed to have interesting biological or medicinal properties[12,17]. It has been isolated from the roots of *Liriope spicata*[17], used in Chinese natural medicine, and this fructoside was found to surpress IgE antibody formation. Recently, it has been also prepared in an efficient manner using a different route[15]. Acetylation of the butyl α-D-fructofuranoside **26** afforded the pure corresponding peracetate **27**. The two-step procedure described is a possible route to other alkyl fructosides with the furanosides as the main products. The results indicate that under the applied conditions the high degree of fructofuranosides formed in the first step is maintained in the second transglycosidation step. The ring-size of the five-membered furanoside ring seems to have been maintained. This phenomenon has been demonstrated previously in a transglycosidation reaction of benzyl fructofuranosides in ethanol which showed preponderant formation of an anomeric mixture of D-fructosides having the same ring-size as the starting material[25].

The same two-step procedure used for n-butanol was then applied to 1-octanol. Although the reaction temperature in the transglycosidation step was raised to 50°C a longer reaction time (7 days)

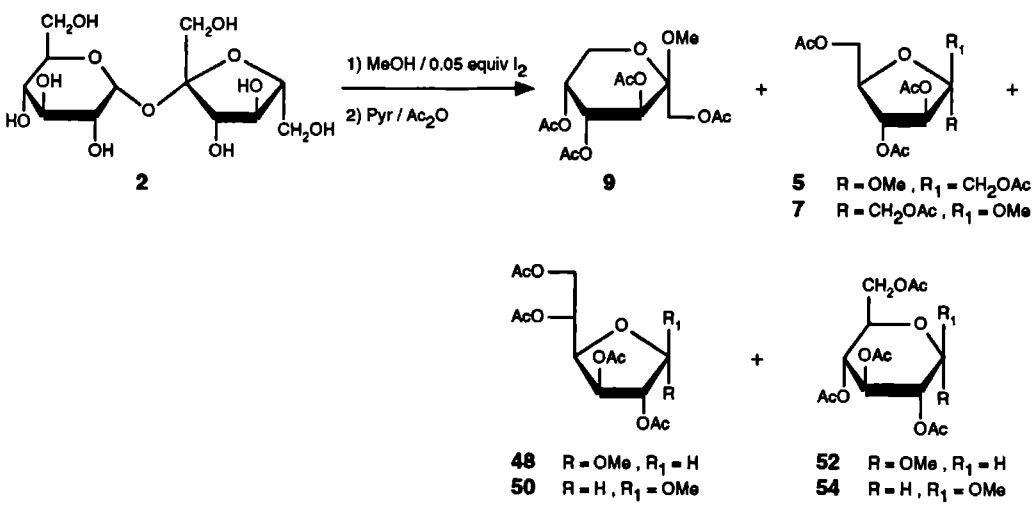
was required to obtain the octyl fructosides **32**, **34** and **36** in reasonable to moderate yield (39%). At this stage the limitatations of the iodine-catalyzed glycosidation reactions seemed to have been reached.

The use of another catalyst, *e.g.* BF_3-methanolate, in the second transglycosidation step showed some improvement. Use of this catalyst in the second step of the reaction demonstrated that the reaction time could be shortened to 1-2 h and that octyl fructosides were then obtained in 40% overall yield.

With inulin (**3**) as starting material this two-step reaction afforded the octyl fructosides in more moderate yields (25%). It was noteworthy that in this reaction only the octyl α-D-fructofuranoside (**32**) and octyl β-D-fructofuranoside (**34**) were formed and these could be separated using column chromatography. The expected by-product octyl β-D-fructopyranoside (**36**) could not be detected.

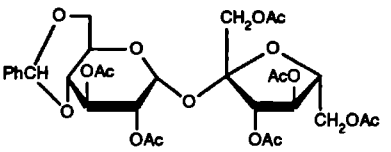
The iodine-catalyzed glycosidation reaction was also investigated with sucrose (**2**). This disaccharide contains two different building blocks, *i.e.* D-glucose and D-fructose, and glycosides of both sugars would be expected (Scheme 3).

Scheme 3 *Glycosidation of sucrose.*

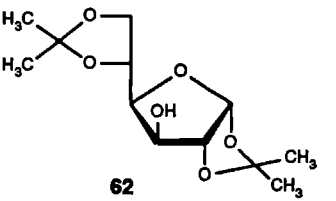


Sucrose (**2**) in boiling methanol was treated with a catalytic amount of iodine and after processing and standard acetylation of the crude product mixture analysis (GLC, NMR) indicated that a mixture of the acetylated fructosides (**5**, **7** and **9**) and glucosides (**48**, **50**, **52** and **54**) was obtained. This reaction demonstrates that glycosidation is possible under the applied conditions, and that sucrose is cleaved to give the two monosaccharides which subsequently yield a mixture of the corresponding glycosides. No cleavage of this interglycosidic bond was previously reported[22] during

the debenzylidenation of 4,6-*O*-benzylidene-sucrose hexaacetate (**46**) by methanol in the presence of iodine. It is possible that the deactivating effect of the acetate groups on **46** may have been responsible for this contradictory result.



46



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The iodine-catalyzed glycosidation reaction of D-fructose described here represents a novel method for the synthesis of alkyl fructofuranosides. The procedure is simple and in most cases the pure α-D-fructofuranosides can be readily isolated. The scope seems to be limited to shorter alcohols, and for longer alcohols an indirect transglycosidation procedure must be utilized.

5.3 Iodine-catalyzed glycosidation reactions of D-glucose

5.3.1 *Iodine-catalyzed glycosidation of D-glucose*

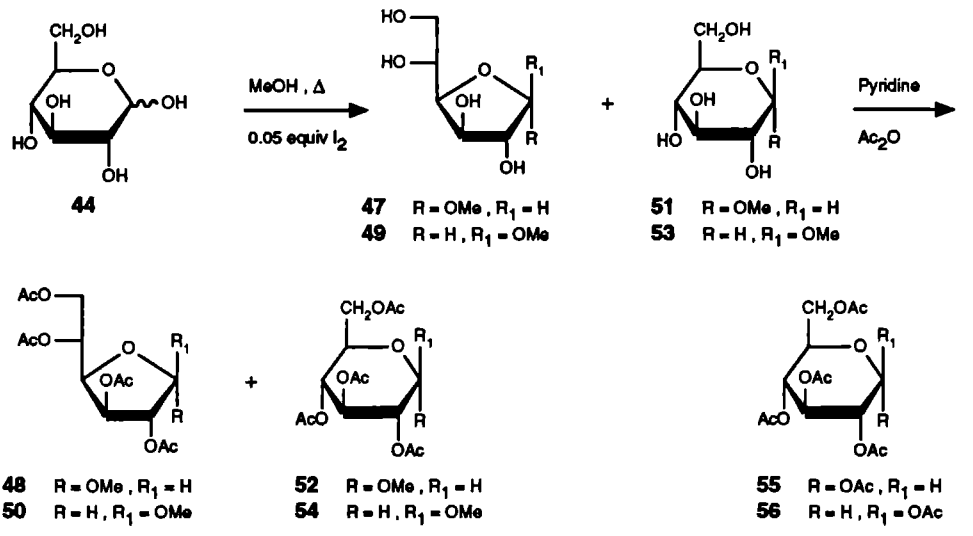
The direct glycosidation of D-glucose (**44**) has been studied extensively, mainly using the Fischer procedure (section 5.2.1). Normally the acid-catalyzed glycosidation of **44**, although simple to perform, is a complex reaction leading to several products and can be performed only with simple liquid alcohols. As with D-fructose (**1**), complex anomeric mixtures of furanosides and pyranosides result and only by appropiate selection of the reaction conditions preponderant formation of either furanosides or pyranosides can be achieved. In the early stages, under mild conditions, the glycosidation is kinetically controlled and yields mainly mixtures of the two furanosides. Under more vigorous conditions, *e.g.* boiling, thermodynamic control is achieved and pyranosides are then favoured. The anomeric effect which favours the formation of the axial C-1 form of the glycoside usually ensures that the α-D-hexopyranosides are preponderant which can often be separated from the cooled reaction mixture by their ready crystallization. Performance of the Fischer glycosidation procedure under strictly kinetic controlled conditions can give access to the preparation of alkyl D-glycofuranosides[10].

Furanosides are prepared frequently from sugar derivatives protected in the furanoid form. D-Glucose for example, can be transformed into an alkyl D-glucofuranoside *via* 1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-carbonate. A disadvantage of this route is the use of phosgene as reagent which causes considerable environmental and toxicity problems. An alternative route to D-glucofuranosides is based on the facile acid catalyzed glycosidation of D-glucurono-3,6-lactone by alcohols. The alkyl D-glucofuranosidurono-3,6-lactones derived in this way are then readily reduced by sodium borohydride[31] to afford anomeric forms of alkyl D-glucofuranosides.

Dilute solutions of iodine in methanol have been used as an acetal deprotection method[20] of various carbohydrate acetals, as already discussed in section 5.2.1. In this method relatively high concentrations of iodine were used at reflux temperature (0.18 equiv, 0.5% w/v) or at room temperature (0.35 equiv, 1% w/v) to afford mixtures of methyl glycofuranosides as the main products. In a typical example treatment of the 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**62**) with iodine in boiling methanol for 4 h yielded methyl α-D-glucofuranoside (**47**, 42%), methyl β-D-glucofuranoside (**49**, 46%) and methyl α-D-glucopyranoside (**51**, 12%) as products, respectively.

The direct glycosidation of D-glucose was investigated using the same methodology as described earlier for D-fructose, *i.e.* with low catalytic amounts of iodine in methanol as the reagent (Scheme 4). Various aspects of these reactions are described.

Scheme 4 *Glycosidation of D-glucose.*



When D-glucose was treated with a catalytic amount of iodine (0.05 equiv) in boiling methanol for 40 h, analysis (TLC, solvent A) indicated the presence of four products, with mobilities expected for the glycosides which were divided into a relatively fast moving major spot-area and a slower moving minor spot-area. The isolated product mixture was acetylated in the usual manner (acetic anhydride - pyridine). GLC-analysis of this product mixture revealed the presence of four individual components which were identified as the peracetates of methyl α-D-glucofuranoside (**48**, 31%), methyl β-D-glucofuranoside (**50**, 48%), methyl α-D-glucopyranoside (**52**, 3%) and methyl β-D-glucopyranoside (**54**, 4%), together with α/β-D-glucopyranose penta-acetate (14%). Identification of these products was further substantiated using ^{13}C-NMR spectroscopy. The structures of the glucosides were assigned on basis of the characteristic signals assigned to the anomeric C-1 atoms, and by comparison with the defined chemical shifts noted in the literature[24].

The result demonstated that for D-glucose the D-glucofuranosides are the major products in this type of glycosidation reaction, and that the D-glucopyranosides are formed only as minor products. This result was very similar to that found for the iodine-catalyzed methanolysis of D-fructose (**1**) where the furanosides also clearly preponderated in the obtained reaction mixtures. The result is comparable with those obtained by the acetal deprotection method[20] described above for the di-*O*-isopropylidene derivative of glucose which afforded also a product mixture containing 90% of furanosides, although with use of much higher amounts of iodine.

The crude reaction product from the glycosidation reaction of D-glucose with methanol in the presence of catalytic iodine could be purified directly by column chromatography. Isolation of the major products with the highest mobilities (TLC) in this manner afforded a mixture consisting of methyl α-D-glucofuranoside (**47**) and methyl β-D-glucofuranoside (**49**) in 66% yield which were characterised after acetylation as a mixture of the corresponding acetates **48** and **50** (ratio 50:50). The minor products with lower mobilties (TLC) most logically should be the methyl α-D-glucopyranoside (**51**) and the methyl β-D-glucopyranoside (**53**), respectively.

In comparison with the iodine-catalyzed glycosidation reaction of D-fructose much longer (40 h) reaction times are required for D-glucose. Further analysis (GLC, NMR) of the acetylated product mixture of the glycosidation of D-glucose in methanol revealed the presence (14%) of α-D-glucopyranose penta-acetate (**55**) and β-D-glucopyranose penta-acetate (**56**). These products result from a small amount of unreacted D-glucose (**44**) in the reaction mixture. The lower reactivity of D-glucose compared with D-fructose under the glycosidation conditions described above is possibly due to the fact that D-fructose is able to form a more reactive intermediate, namely a tertiary carbonium ion at the anomeric C-2 which is not possible for D-glucose. Extension of the reaction time of **44** in boiling methanol with 0.05 equiv of iodine to 64 h resulted in a product mixture, which after acetylation, was shown to contain the methyl D-glucosides **48**, **50**, **52** and **54** in essentially the same ratio (32:50:7:6), but still containing small amounts (5%) of the D-glucose penta-acetates. Raising the concentration of iodine from 0.05 to 0.10 equiv proved to be more effective in obtaining a complete glycosidation. Treatment of **44** with boiling methanol containing iodine (0.10 equiv) for 30 h, followed subsequently by acetylation, gave the methyl D-glucosides **48**, **50**, **52** and **54** in almost the same ratio (34:56:4:5) but with only trace amounts (1%) of the by-products **55** and **56**.

The iodine-catalyzed glycosidation reaction of D-glucose described here represents a further extension of this novel method for the synthesis of alkyl D-glycofuranosides.

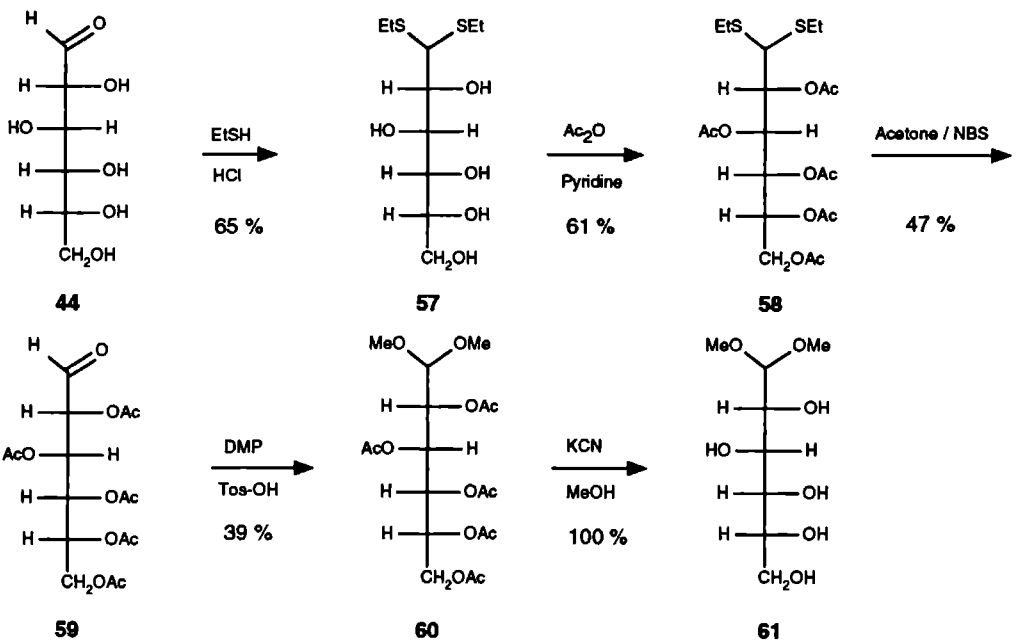
5.3.2 *The possible role of glucose dimethyl acetal in the iodine-catalyzed glycosidation of D-glucose*

The precise mechanism of the initial reaction of aldoses to yield furanosides is not known fully, although sensible assumptions can be made[8]. In this respect the acyclic dimethyl acetals were proposed initially by Fischer[19] (1895) as possible glycoside precursors, specifically for the furanosides. It is of considerable interest that the dimethyl acetals of D-xylose and D-glucose have

been shown to be present in the initial stages of glycosidation reactions[32]. In the present study (section 5.3.1) trace amounts (0-1.5%) of the dimethyl acetal of D-glucose (**60**) could be detected, in some cases, in the acetylated product mixtures of the iodine-catalyzed glycosidation of D-glucose in methanol.

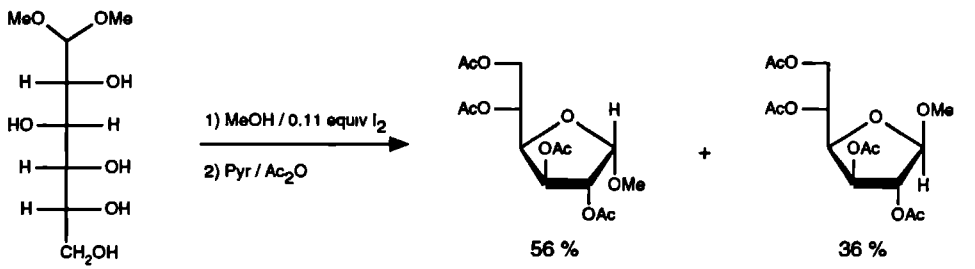
Although acyclic diacetals are thought to be potential intermediates in the glycosidation of carbohydrates, sometimes difficulties have been encountered in finding evidence for their existence using gas-chromatographic procedures[33]. It is possible that these acetals are masked by cyclic products, as the presence of the dimethyl acetals in the methanolysis of D-xylose and D-glucose has been reported using isotopic labelling methods[32]. It was found in these studies[32] that the dimethyl acetal concentration never exceeded 2.5% at anyone time in either case. When the furanosides are present in maximum amounts, the diacetal concentration builds up to *ca* 2.5%, and then decreases as pyranosides are formed, and the concentration remains at only 1% at equilibrium. Examination of the initial stages of the methanolysis of D-glucose revealed that the furanosides are formed initially, with the α-form preponderating, and that the acyclic diacetal is formed in only minor proportions and is not a major component even in the early stages of the reaction. It was concluded that the acyclic diacetals were not the precursors from which the furanosides were derived, and that they are formed as kinetic products concurrent with the furanosides. The exact role of the dimethyl acetal, is therefore still not clear and a subject of much debate.

Scheme 5 *Synthesis of D-glucose dimethyl acetal (61).*



The iodine-catalyzed glycosidation of D-glucose yielded preponderantly D-glucofuranosides. To investigate the possible role of the D-glucose dimethyl acetal (**61**) in this reaction this compound was prepared using previously described procedures. Treatment of D-glucose (**44**) with ethanethiol[34] gave the known dithioacetal **57**, which was acetylated in the usual manner to give the corresponding acetate **58**. Oxidative removal of the dithioacetal protecting group of the penta-acetate (**58**) with *N*-bromosuccinimide in aqueous acetone solution[35] provided the *aldehydo*-D-glucose penta-acetate (**59**) in reasonable yield (47%). The sensitive *aldehydo* compound **59** was then treated at room temperature with 2,2-dimethoxypropane containing a trace amount of *p*-toluenesulphonic acid[36] to afford the dimethyl acetal penta-acetate **60** (39%). In the final step acetate **60** was deacetylated with a catalytic amount of KCN in methanol[37] to afford the required dimethylacetal (**61**).

Scheme 6 *Glycosidation of D-glucose dimethyl acetal (61).*



61 **48** **50**

56 % 36 %

To investigate the reactivity of the dimethyl acetal of D-glucose in the iodine-catalyzed glycosidation reaction, it was subjected to the same conditions of glycosidation in methanol as for D-glucose (Scheme 6). When the dimethyl acetal **61** was treated with a catalytical amount of iodine (0.06 equiv) in boiling methanol for 29 h, analysis (TLC, GLC) indicated almost exclusively the presence of unreacted compound **61**, with only traces of glycosidic products. Treatment of **61** with a higher concentration of iodine (0.11 equiv) in boiling methanol for 40 h, however, caused complete reaction. The product mixture was acetylated in the usual manner and GLC-analysis of the acetylated product mixture demonstrated the presence of two main individual components. These were identified as methyl α-D-glucofuranoside **48** (56%) and methyl β-D-glucofuranoside **50** (36%), together with a small amount of unreacted dimethyl acetal **60** (7%) and trace amounts of D-glucose peracetates (0-1%). The acetylated product mixture was also analysed by ^{13}C-NMR spectroscopy using an inverse gate decoupling technique[38] (IGDE, T_1= 25s). This ^{13}C-NMR spectrum showed the presence of the signals expected for the designated anomeric carbon atoms assigned to compounds **48** (δ(C-1): 101.1 ppm), **50** (δ(C-1): 107.5 ppm), and **60** (δ(C-1): 102.6 ppm). Integration of the ^{13}C signals gave an indication of the product ratio, **48**: **50**, which was shown to be 57:40 and was in good agreement with the above GLC-analysis.

From these results it can be concluded that the iodine-catalyzed glycosidation of the dimethyl acetal **61**, followed by acetylation, leads almost exclusively to a mixture of the two methyl D-glucofuranosides **48** and **50** in which the α-furanoside **48** preponderates. The reactivity of the dimethyl acetal **61** is somewhat lower compared with the direct glycosidation of D-glucose catalyzed by iodine. The obtained results are also in agreement with the mechanistic arguments presented previously[8], and in particular with the observations of a detailed investigation on the hydrolysis of the acyclic dimethyl acetals of D-glucose and D-galactose in dilute (0.05 M) aqueous hydrochloric acid[39]. Under these conditions, apart from undergoing hydrolysis to D-glucose and D-galactose, the acyclic acetals also yielded mixtures of the α- and β-furanosides in high yields by concurrent ring closure. The kinetically controlled yields of furanosides for the D-glucose and D-galactose acetals were 98 and 71%, respectively, which showed the successful competition, in each case, of the C-4 hydroxyl group over the solvent. A concerted mechanism was suggested which involved simultaneous ring closure with breaking of the acetal bond. This was supported by the observation that the product from the D-glucose acetal contains a much higher proportion of furanosides, and that k_{total} for the D-glucose acetal is much greater than for the D-galactose acetal[39]. The acid catalyzed ring closure of these dimethyl acetals to furanosides was also investigated in methanolic solution. Methanolysis of **61** under these conditions[39] gave the methyl α-furanoside **48** and the methyl β-furanoside **50** after acetylation in a ratio of 73:23, which is also similar to the result of the present study. It was noted further that five-membered rings are normally formed more rapidly than the corresponding six-membered ones from saturated acyclic compounds. In particular, the cyclization of acyclic D-glucose, D-galactose and D-arabinose acetals yields furanosides at least 200 times more rapidly than the thermodynamically more stable pyranosides. Very recently, the synthesis of D-glucose dialkyl acetals and dodecyl D-glucofuranosides was described[40] which were claimed to have good amphipfilic and liquid-crystalline properties. Dodecyl α- and β-D-glucofuranoside were prepared by treatment of D-glucose didodecyl acetal, obtained in essentially the same way as described above, with dodecanol in the presence of methanesulphonic acid.

It is difficult to conclude from these results the precise role of the acyclic dimethyl acetal of D-glucose in the iodine-catalyzed glycosidation reactions. It is noteworthy that only the methyl furanosides are formed in the glycosidation of the dimethyl acetal, whilst the same reaction conditions are used as for the direct glycosidation of D-glucose, and this possibly indicates that the dimethyl acetal is a precursor of the furanosides. If the dimethyl acetal is only a kinetic by-product in these glycosidations then the possible formation of pyranosides would have been expected. This was not observed in the present study. The absence of water could be another important factor in this process. It is of particular interest to note here that the attempted formation of the dimethyl acetal **60** by treatment of the aldehyde peracetate **59** with a solution of iodine in methanol was unsuccessful. This may have been due to the unfavourable formation of water during this reaction. This may have caused the hydrolysis of the sensitive diacetal **60** to the parent compound **59**. The successful conditions used for the synthesis of compound **60**, *e.g.* 2,2-dimethoxypropane containing catalytic

p-toluenesulphonic acid, would have circumvented this problem because 2,2-dimethoxypropane is known to be a very effective dehydrating agent[41]. Further mechanistic studies of these aspects would be required to fully clarify the events.

5.4 Concluding remarks

It has been demonstrated that the direct iodine-catalyzed glycosidation reactions with D-fructose, D-glucose, inulin and sucrose could be utilized as a novel method for the synthesis of alkyl D-glycofuranosides. The procedures are simple and in general a much greater control of product ratios was possible compared with the standard Fischer procedure.

For D-fructose the glycosidation procedure led to the efficient formation of D-fructofuranosides and in most cases the pure α-D-fructofuranosides could be readily isolated. The scope of the reaction seems to be limited for shorter alcohols, for longer alcohols an indirect transglycosidation procedure must be utilized.

The iodine-catalyzed glycosidation of D-glucose showed a somewhat lower reactivity but led to an efficient synthesis of methyl D-glucofuranosides. The D-glucose dimethyl acetal **61** probably has an important role in this reaction; the iodine-catalyzed glycosidation of this acetal led exclusively to an anomeric mixture of the methyl D-glucofuranosides.

5.5 Experimental

General methods

Optical rotations were determined with a Perkin-Elmer automatic polarimeter, model 241 MC on 1% solutions at 20°C in the solvents indicated. Thin-layer chromatography (TLC) on pre-coated plates of silica gel (Merck) was performed with dichloromethane - methanol (4/1, v/v, solvent A) or hexane - ethyl acetate (1/1, v/v, solvent B). Detection was affected by spraying with 3% H_2SO_4 in ethanol followed by heating at 140°C. Column chromatography was performed on Silica gel 60 (Merck) with the eluents indicated. GLC was performed with a Hewlett-Packard 5890 series II gaschromatograph, using a capillary column (25m) of medium polarity (PAS 1701), a temperature program from 100-250°C at 15°C/min, followed by 10 min at 250°C (isothermal), and nitrogen as the carrier gas (2 ml/min). Compounds were identified by co-injection with authentic samples and the percentages composition of the analysed mixtures are all relative. ^{1}H-NMR spectra were recorded with a Bruker AC 100 (100 MHz) or Bruker AM 400 (400 MHz) spectrometer on solutions in $CDCl_3$ (internal standard Me_4Si) or D_2O. ^{13}C-NMR spectra were recorded with a Bruker AC 100 or Bruker AM 400 spectrometer operating at 25 and 100.6 MHz, respectively, on solutions in $CDCl_3$ (internal Me_4Si) or D_2O (external dioxane at 76.8 ppm). Melting points were determined on a Reichert thermopan microscope and are uncorrected. Mass spectra were recorded using a double focussing VG 7070E mass spectrometer. The chemical ionisation (CI) technique was used with methane as reaction gas and the fast atom bombardment (FAB) technique (xenon atoms).

Inulin, (ex dahlia tubers) purchased from Sigma Chemicals was powdered finely and dried *in vacuo* (80^0C, 15 mm) prior to use.

Reaction of methanol containing iodine with :

(a) *D-Fructose* (**1**). A stirred suspension of D-fructose (**1**, 1000 mg, 5.55 mmol) in methanol (50 ml) was treated with iodine (70 mg, 0.28 mmol, 0.05 equiv) and the mixture was heated under reflux for 3 h, whereon a clear solution was obtained. The cooled mixture was treated with solid sodium thiosulphate until colourless, filtered and concentrated *in vacuo* to give a colourless syrup. Column chromatography (dichloromethane / methanol, 9:1) of the crude product afforded pure compound **4** (319 mg, 29.6%) and a mixture of **6** and **8** (663 mg, 61.5%). Treatment of the products under standard conditions of acetylation with acetic anhydride and pyridine in the usual manner afforded the corresponding peracetates as colourless syrups.

In this manner acetylation of **4** gave pure **5** (569 mg, 96%), $[\alpha]_D$ $+81.4^0$ ($CHCl_3$), lit.[29] $[\alpha]_D$ $+88.1^0$. GLC analysis: R_t 11.17 98%. ^{1}H-NMR ($CDCl_3$): δ 5.30 (d, 1H, $J_{3,4}$ 1.9 Hz, H-3), 4.94 (dd, 1H, $J_{4,3}$ 1.9 Hz, $J_{4,5}$ 5.0 Hz, H-4), 4.45 (dd, 1H, $J_{6a,6b}$ 11.6 Hz, $J_{6a,5}$ 3.1 Hz, H-6a), 4.43 (d, 1H, $J_{1a,1b}$ 12.2 Hz, H-1a), 4.21 (d 2nd order, 1H, $J_{6b,6a}$ 11.6 Hz, $J_{6b,5}$ 0-1 Hz, H-6b), 4.16 (m, 1H, $J_{5,4}$ 5.0 Hz, $J_{5,6a}$ 3.1 Hz, $J_{5,6b}$ 0-1 Hz, H-5), 4.12 (d, 1H, $J_{1b,1a}$ 12.2 Hz, H-1b), 3.32 (s, 3H, OCH_3), 2.10 (s, 12H, CH_3 acetyl) ppm. ^{13}C-NMR ($CDCl_3$, DEPT-135): δ 170.38, 169.97 (2x), 168.67 (C=O acetyl), 106.76 (C-2), 80.18, 79.51, 78.04 (C-3, C-4 and C-5), 63.04, 58.10 (C-6 and C-1), 48.58 (OCH_3), 20.58 (CH_3 acetyl) ppm. Acetylation of the combined fraction of **6** and **8** gave **7** and **9** (816 mg, 66%). GLC analysis: R_t 11.37 (**7**, 80%) and R_t 11.62 (**9**, 17%). ^{1}H-NMR ($CDCl_3$): δ 5.7-3.8 (m, 7H, carbohydrate skeleton), 3.35 (s, 3H, OCH_3) 2.10 (s, 20H, CH_3 acetyl) ppm. ^{13}C-NMR ($CDCl_3$): δ C-2 signals for compounds **7** and **9** detected at 102.66 and 98.76 ppm, respectively.

In another experiment a stirred suspension of D-fructose (**1**, 1000 mg, 5.55 mmol) in methanol (50 ml) containing iodine (70 mg, 0.28 mmol, 0.05 equiv) was heated under reflux for 2 h and then processed as decribed above. The crude reaction mixture was not purified but acetylated directly with pyridine (10 ml) and acetic anhydride (5 ml) in the usual manner to afford a mixture of compounds **5**, **7**, and **9** (2 g, 99%) as a syrup. GLC analysis: R_t 11.08 (**5**, 47%), R_t 11.29 (**7**, 43%), R_t 11.54 (**9**, 10%). ^{13}C-NMR ($CDCl_3$): δ C-2 signals for compounds **5**, **7** and **9** were detected at 106.75, 102.61 and 98.72 ppm, respectively.

In another experiment a stirred suspension of D-fructose (**1**, 1000 mg, 5.55 mmol) in methanol (50 ml) was heated under reflux to a clear solution for 30 min (pre-equilibration), iodine (70 mg, 0.28 mmol, 0.05 equiv) was added and then the reaction mixture was heated under reflux for 2 h and then processed as decribed above. The crude reaction mixture was acetylated in the usual manner to afford a mixture of compounds **5**, **7**, and **9** (2 g, 99%) as a syrup. GLC analysis: R_t 11.12 (**5**, 50%), R_t 11.33 (**7**, 41%), R_t 11.57 (**9**, 9%). ^{13}C-NMR ($CDCl_3$): δ C-2 signals for compounds **5**, **7** and **9** were observed at 106.67, 102.74 and 98.64 ppm, respectively.

(b) *Inulin* (**3**). A stirred mixture of inulin (**3**, 1000 mg) suspended in methanol (50 ml) containing iodine (70 mg, 0.28 mmol, 0.05 equiv) was heated under reflux for 3 h and the resulting clear solution processed as described above in (a). The crude product mixture was acetylated in the usual manner to afford a mixture of compounds **5**, **7** and **9** (1850 mg, 92%) as a syrup. GLC analysis: R_t 11.06 (**5**, 45%), R_t 11.27 (**7**, 46%), R_t 11.52 (**9**, 9%). ^{13}C-NMR ($CDCl_3$): δ C-2 signals for compounds **5**, **7** and **9** detected at 106.77, 102.63 and 98.73 ppm, respectively.

Reaction of ethanol containing iodine with :

(a) *D-Fructose* (**1**). A stirred suspension of D-fructose (**1**, 1000 mg, 5.55 mmol) in ethanol (50 ml) was treated with iodine (70 mg, 0.28 mmol, 0.05 equiv) and the mixture was heated under reflux for 2 h, whereon a clear solution was obtained. The cooled mixture was treated with sodium thiosulphate until colourless, filtered and concentrated *in vacuo* to give a colourless syrup. Column chromatography (dichloromethane / methanol, 9:1) of the crude product afforded pure compound **10** (385 mg, 33.3%), and a mixture of **12** and **14** (484 mg, 42%). Treatment of **10** under standard conditions of acetylation with pyridine (3 ml) and acetic anhydride (2 ml) afforded pure **11** (610 mg, 88%) as a syrup. $[\alpha]_D$ +82^0 ($CHCl_3$); Lit.[29] $[\alpha]_D$ +76^0. GLC analysis: R_t 11.13 97%. ^{1}H-NMR ($CDCl_3$): δ 5.32 (d, 1H, $J_{3,4}$ 1.8 Hz, H-3), 4.93 (dd, 1H, $J_{4,3}$ 1.8 Hz, $J_{4,5}$ 4.9 Hz, H-4), 4.43 (dd, 1H, $J_{6a,6b}$ 11.2 Hz, $J_{6a,5}$ 3.7 Hz, H-6a), 4.41 (d, 1H, $J_{1a,1b}$ 12.1 Hz, H-1a), 4.21 (d 2nd order, 1H, $J_{6b,5}$ 0-1 Hz, H-6b), 4.18 (m, 1H, $J_{5,4}$ 4.9 Hz, H-5), 4.12 (d, 1H, $J_{1b,1a}$ 12.1 Hz, H-1b), 3.61 (m, 2H, $OC\underline{H}_2CH_3$), 2.10 (s, 12H, CH_3 acetyl), 1.20 (t, 3H, $OCH_2C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$, DEPT-135): δ 170.38, 169.94 (2x), 168.67 (C=O acetyl), 106.60 (C-2), 80.23, 79.50, 78.02 (C-3, C-4 and C-5), 63.11, 58.90, 56.66 (C-6, C-1 and $O\underline{C}H_2CH_3$), 20.56 (CH_3 acetyl), 15.13 ($OCH_2\underline{C}H_3$) ppm. A sample (100 mg) of the mixture of compounds **12** and **14** was crystallized from ethanol to afford pure **14** (15 mg), m.p. 151-152^0 C, $[\alpha]_D$ -151^0 (MeOH); lit.[12] m.p. 150-151^0 C, $[\alpha]_D$ -136^0.

In another experiment a stirred suspension of D-fructose (**1**, 1000 mg, 5.55 mmol) in ethanol (50 ml) containing iodine (70 mg, 0.28 mmol, 0.05 equiv) was heated under reflux for 2 h, then processed as decribed above and acetylated in the usual manner to afford a mixture of compounds **11**, **13**, and **15** (1.7 g, 80%) as a syrup. GLC analysis: R_t 11.16 (**11**, 36%), R_t 11.27 (**13**, 28%), R_t 11.48 (**15**, 35%). ^{13}C-NMR ($CDCl_3$): δ C-2 resonances for compounds **11**, **13** and **15** occurred at 106.67, 103.08 and 98.95 ppm, repectively.

In another experiment a stirred suspension of D-fructose (**1**, 1000 mg, 5.55 mmol) in ethanol (50 ml) containing iodine (70 mg, 0.28 mmol, 0.05 equiv) was heated at 65^0 C for 3 h, then processed as decribed above and acetylated in the usual manner to afford a mixture of compounds **11**, **13**, and **15** (1.9 g, 90%) as a syrup. GLC analysis: R_t 11.18 (**11**, 57%), R_t 11.29 (**13**, 37%), R_t 11.45 (**15**, 6%). ^{13}C-NMR ($CDCl_3$): δ C-2 signals for compounds **11**, **13** and **15** appeared at 106.56, 102.95 and 98.89 ppm, respectively.

In another experiment a stirred suspension of D-fructose (**1**, 4000 mg, 22.20 mmol) in ethanol (200 ml) was treated with iodine (560 mg, 2.22 mmol, 0.10 equiv) and set aside at room temperature for 7 days. The clear solution that was obtained was processed as described above. Column

chromatography (dichloromethane / methanol, 9:1) of the resultant residue gave pure compound **10** (1407 mg, 30.4%, $[\alpha]_D$ +75^0 (H_2O), lit.[29] $[\alpha]_D$ +65^0) and two mixtures of **12** and **14** (1310 mg, 28% and 564 mg, 12%). Acetylation of both mixtures in the usual manner gave mixtures of **13** and **15** (1267 mg, 54% and 652 mg 64%) as syrups. GLC analysis (first mixture): R_t 11.35 (**13**, 85%), R_t 11.52 (**15**, 12%). GLC analysis (second mixture): R_t 11.27 (**13**, 86%), R_t 11.43 (**15**, 13%). ^{1}H-NMR ($CDCl_3$): δ 5.6-3.8 (m, 7H, carbohydrate skeleton), 3.58 (m, 2H, $OC\underline{H}_2CH_3$), 2.10 (s, 20H, CH_3 acetyl), 1.20 (t, 3H, $OCH_2C\underline{H}_3$) ppm. ^{13}C-NMR (100 HHz): δ C-2 signals for compounds **13** and **15** appeared at 103.07 and 98.93 ppm, respectively.

For comparative reasons a sample (500 mg) of authentic compound **14**[15] was acetylated with pyridine (5 ml) and acetic anhydride (3.5 ml) and processed in the usual manner to give pure **15** (896 mg, 99%) as a syrup, $[\alpha]_D$ -124^0 ($CHCl_3$), lit.[30] $[\alpha]_D$ -128^0. GLC analysis: R_t 11.47 100%. ^{1}H-NMR ($CDCl_3$): δ 5.52 (d, 1H, $J_{3,4}$ 10.1 Hz, H-3), 5.36 (m, 1H, H-5), 5.33 (dd, $J_{4,5}$ 3.5 Hz, $J_{4,3}$ 10.2 Hz, H-4), 4.30 (d, 1H, $J_{1a,1b}$ 11.8 Hz, H-1a), 4.08 (d, 1H, $J_{1b,1a}$ 11.8 Hz, H-1b), 3.89 (d, 1H, $J_{6b,6a}$ 12.9 Hz, H-6b), 3.81 (dd, 1H, $J_{6a,6b}$ 12.9 Hz, $J_{6a,5}$ 1.5 Hz, H-6a), 3.63 (m, 2H, $OC\underline{H}_2CH_3$), 2.17, 2.11, 2.08, 1.98 (4s, 12H, CH_3 acetates), 1.26 (t, 3H, $OCH_2C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$, DEPT-135): δ 170.27, 170.14, 170.00, 169.83 (C=O acetyl), 98.93 (C-2), 68.90, 68.35, 67.32 (C-3, C-4 and C-5), 62.71, 61.78, 57.12 (C-6, C-1 and $O\underline{C}H_2CH_3$), 20.90, 20.67, 20.57 (CH_3 acetates), 15.28 ($OCH_2\underline{C}H_3$) ppm.

A cooled (0^{0}C), stirred solution of compound **10** (671 mg, 3.22 mmol) in pyridine (10 ml) was treated with trityl chloride (1977 mg, 6.44 mmol) and set aside at room temperature for 7 days. The reaction mixture was poured into ice water (150 ml). The product mixture was extracted (2x) with dichloromethane (80 ml). The organic layer was washed successively with 2M HCl (2 x 50 ml), saturated aqueous sodium hydrogen carbonate (2 x 50 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (hexane / ethyl acetate, 3:1 / 1:1) of the solid residue gave **16** (867 mg, 40%) and **18** (371 mg, 26%) as pure compounds. Both compounds were acetylated with pyridine (5 ml) and acetic anhydride (4 ml) in the usual manner.

In this manner acetylation of **16** gave crystalline **17** upon treating the reaction mixture with ice water. The crude product was washed several times with water, dried *in vacuo* (872 mg, 90%) and a sample of the crude product was recrystallized from ethanol to give pure **17** as an ethanolate, m.p. 80-83^0 C, $[\alpha]_D$ +43.5^0 ($CHCl_3$); lit.[29] m.p. 142-144^0 C, $[\alpha]_D$ +44.7^0. Calculated for $C_{50}H_{48}O_8$.EtOH (821.94): C 75.98%, H 6.50%; Found: C 76.08% H 6.45%. FAB-MS: *m/z* 799 (M^+ + Na), 731 (M^+ - OC_2H_5), 699 (M^+ - C_6H_5), 503 (M^+ - $OCH_2C(C_6H_5)_3$), 243 (M^+ - 2 $OCH_2C(C_6H_5)_3$). ^{1}H-NMR ($CDCl_3$): δ 7.16-7.44 (m, 30H, trityl), 5.49 (d, 1H, $J_{3,4}$ 0-1 Hz, H-3), 4.31 (dd, 1H, $J_{4,5}$ 4.3 Hz, H-4), 3.96 (dd, 1H, $J_{6a,6b}$ 9.1 Hz, $J_{6a,5}$ 4.5 Hz, H-6a), 3.42 (d, 1H, $J_{1a,1b}$ 9.6 Hz, H-1a), 3.40 (d 2nd order, 1H, $J_{6b,5}$ 0-1 Hz, H-6b), 3.30 (m, 1H, $J_{5,4}$ 4.4 Hz, H-5), 3.19 (d, 1H, $J_{1b,1a}$ 9.8 Hz, H-1b), 3.25 (m, 2H, $OC\underline{H}_2CH_3$), 2.07 and 1.77 (s, 2x3H, CH_3 acetyl), 1.20 (t, 3H, $OCH_2C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$, DEPT-135): δ 169.92, 168.92 (C=O acetyl), 143.82, 143.52 (q-C trityl), 129-127 (aromatic, trityl), 107.70 (C-2), 81.92, 80.00, 78.55 (C-3, C-4 and C-5), 63.70,

59.91, 55.91 (C-6, O<u>C</u>H_2CH_3 and C-1), 20.82 (CH_3 acetyl), 15.16 ($OCH_2\underline{C}H_3$) ppm. Acetylation of **18** gave **19** upon treatment of the reaction mixture with ice water. The crude product was extracted with dichloromethane and processed as described above to afford compound **19** as an oil which crystallized on standing (379 mg, 84%). Recrystallization (2-propanol) gave pure crystalline **19** (304 mg, 64%), m.p. 127-128^0 C, $[\alpha]_D$ +62.8^0 ($CHCl_3$). Calculated for $C_{33}H_{36}O_9$ (576.62): C 68.74%, H 6.29%; Found: C 68.76%, H 6.30%. FAB-MS: *m/z* 576 (M^+), 599 (M^+ + Na), 531 (M^+ - OC_2H_5), 499 (M^+ - C_6H_5), 303 (M^+ - $OCH_2C(C_6H_5)_3$). ^{1}H-NMR ($CDCl_3$, COSY): δ 7.20-7.40 (m, 15H, trityl), 5.32 (d, 1H, $J_{3,4}$ 1.7 Hz, H-3), 5.10 (dd, 1H, $J_{4,3}$ 1.7 Hz, $J_{4,5}$ 5.3 Hz, H-4), 4.42 (d, 1H, $J_{1a,1b}$ 12.1 Hz, H-1a), 4.17 (d, 1H, $J_{1b,1a}$ 12.1 Hz, H-1b), 4.08 (m, 1H, H-5), 3.60 (m, 2H, O<u>C</u>H_2CH_3), 3.36 (m, 2H, H-6a + H-6b), 2.02 (s, 3x3H, CH_3 acetyl), 1.19 (t, 3H, $OCH_2C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$, DEPT-135): δ 170.16, 169.82, 168.83 (C=O acetyl), 143.72 (q-C trityl), 128.7 + 127.7 (2x), 127.0 (aromatic, trityl), 106.38 (C-2), 81.26, 80.17, 78.28 (C-3, C-4 and C-5), 63.12, 59.23, 56.55 (C-6, O<u>C</u>H_2CH_3 and C-1), 20.65 (CH_3 acetyl), 15.27 ($OCH_2\underline{C}H_3$) ppm.

(b) *Inulin* (**3**). A stirred mixture of inulin (**3**, 1000 mg) suspended in ethanol (50 ml) containing iodine (70 mg, 0.28 mmol, 0.05 equiv) was heated under reflux for 4 h and the resulting clear solution processed as described above. Column chromatography (dichloromethane / methanol, 9:1) of the crude product afforded a mixture of the ethyl fructosides **10**, **12** and **14** (277 mg, 24%). The mixture was acetylated with pyridine (6 ml) and acetic anhydride (5 ml) in the usual manner to afford a mixture of compounds **11**, **13** and **15** (333 mg, 66%) as a syrup. GLC analysis: R_t 11.06 (**11**, 37%), R_t 11.27 (**13**, 28%), R_t 11.52 (**15**, 25%). ^{13}C-NMR ($CDCl_3$): δ C-2 signals for compounds **11**, **13** and **15** were detected at 106.65, 103.04 and 98.93 ppm, respectively.

Reaction of D*-fructose* (**1**) *with 1-propanol in the presence of iodine.*

A stirred suspension of D-fructose (**1**, 1000 mg, 5.55 mmol) in 1-propanol (50 ml) was treated with iodine (140 mg, 0.56 mmol, 0.1 equiv) and the mixture was heated at 60^0 C for 6 h, whereon a clear solution was obtained. The cooled mixture was treated with sodium thiosulphate until colourless, filtered and concentrated *in vacuo* to give a colourless syrup. Column chromatography (dichloromethane / methanol, 9:1) of the crude product afforded pure **20** (272 mg, 22.1%) and a mixture of **22** and **24** (507 mg, 41.1%). Acetylation of both products in the usual manner with acetic anhydride and pyridine afforded the corresponding acetates.

Compound **20** yielded pure **21** (435 mg, 91%), $[\alpha]_D$ +78.7^0 ($CHCl_3$). GLC analysis: R_t 11.72 min 92%. ^{1}H-NMR ($CDCl_3$): δ 5.32 (d, 1H, $J_{3,4}$ 1.4 Hz, H-3), 4.91 (dd, 1H, $J_{4,5}$ 3.2 Hz, H-4), 4.43 (dd, 1H, $J_{6a,6b}$ 10.5 Hz, H-6a), 4.41 (d, 1H, $J_{1a,1b}$ 12.1 Hz, H-1a), 4.20 (d 2nd order, 1H, $J_{6b,5}$ 0-1 Hz, H-6b), 4.16 (m, 1H, H-5), 4.13 (d, 1H, $J_{1b,1a}$ 12.2 Hz, H-1b), 3.49 (m, 2H, O<u>C</u>$H_2CH_2CH_3$), 2.10 (s, 12H, CH_3 acetyl), 1.58 (m, 2H, $OCH_2C\underline{H}_2CH_3$), 0.95 (t, 3H, $OCH_2C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$, DEPT-135): δ 170.43, 170.01 (2x), 168.71 (C=O acetyl), 106.67 (C-2), 80.51, 79.43, 78.17 (C-3, C-4 and C-5), 63.20, 62.57, 58.78 (C-6, O<u>C</u>$H_2CH_2CH_3$ and C-1), 22.76 ($OCH_2\underline{C}H_2CH_3$), 20.56 ($CH_3$ acetyl), 10.57 ($OCH_2CH_2\underline{C}H_3$) ppm. The mixture of **22** and **24** afforded a mixture of **23** and **25** (670 mg, 75%). GLC analysis: R_t 11.75 (**23**, 44%) and R_t 11.93 (**25**, 53%). ^{1}H-NMR ($CDCl_3$): δ 5.6-3.8

(m, 7H, carbohydrate skeleton), 3.49 (m, 2H, $OC\underline{H}_2CH_2CH_3$), 2.10 (s, 20H, CH_3 acetyl), 1.61 (m, 2H, $OCH_2C\underline{H}_2CH_3$), 1.20 (t, 3H, $OCH_2CH_2C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ C-2 signals for compounds **23** and **25** were observed at 103.06 and 98.79 ppm, respectively.

For comparative purposes a sample of authentic compound **24**[15] was acetylated with pyridine (5 ml) and acetic anhydride (3.5 ml) and processed as usual to afford pure **25** as a syrup. $[\alpha]_D$ -125^0 ($CHCl_3$). GLC analysis: R_t 11.97 100%. ^{1}H-NMR ($CDCl_3$): δ 5.52 (d, 1H, $J_{3,4}$ 10.3 Hz, H-3), 5.35 (m, 1H, H-5), 5.33 (dd, $J_{4,5}$ 3.4 Hz, H-4), 4.30 (d, 1H, $J_{1a,1b}$ 11.8 Hz, H-1a), 4.09 (d, 1H, $J_{1b,1a}$ 11.8 Hz, H-1b), 3.90 (d, 1H, $J_{6b,6a}$ 12.8 Hz, H-6b), 3.80 (dd, 1H, $J_{6a,6b}$ 12.9 Hz, $J_{6a,5}$ 1.4 Hz, H-6a), 3.47 (m, 2H, $OC\underline{H}_2CH_2CH_3$), 2.17, 2.11, 2.07, 1.98 (4s, 12H, CH_3 acetates), 1.64 (m, 2H, $OCH_2C\underline{H}_2CH_3$), 0.97 (t, 3H, $OCH_2CH_2C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$, DEPT-135): δ 170.27, 170.14, 170.00, 169.83 (C=O acetyl), 98.76 (C-2), 68.88, 68.36, 67.38 (C-3, C-4 and C-5), 63.04, 62.71, 61.71 ($O\underline{C}H_2CH_2CH_3$, C-6 and C-1), 22.94 ($OCH_2\underline{C}H_2CH_3$), 20.87, 20.63 ($CH_3$ acetates), 10.50 ($OCH_2CH_2\underline{C}H_3$) ppm.

Reaction of D*-fructose* (**1**) *with 1-butanol in the presence of iodine.*

A stirred suspension of D-fructose (**1**, 2000 mg, 11.10 mmol) in methanol (100 ml) was treated with iodine (140 mg, 0.56 mmol, 0.05 equiv), the mixture was heated under reflux for 2 h, and the cooled solution was then concentrated *in vacuo*. The resulting syrup was dissolved in 1-butanol (100 ml) and the mixture was allowed to stir at room temperature for 7 days. The reaction mixture was then treated with sodium thiosulphate until colourless, filtered and concentrated *in vacuo* to give a syrup. Column chromatography (dichloromethane / methanol, 9:1) of the crude material afforded pure **26** (455 mg, 17.4%), a mixture of compounds **26**, **28** and **30** (538 mg, 20.5%) and a mixture of compounds **28** and **30** (522 mg, 19.9%).

Acetylation of compound **26** in the usual manner gave the pure peracetate **27** (686 mg, 88%), $[\alpha]_D$ +64.3^0 ($CHCl_3$). GLC analysis: R_t 12.37 87%. ^{1}H-NMR ($CDCl_3$): δ 5.32 (d, 1H, $J_{3,4}$ 1.5 Hz, H-3), 4.91 (dd, 1H, $J_{4,5}$ 4.4 Hz, H-4), 4.43 (dd, 1H, $J_{6a,6b}$ 10.8 Hz, H-6a), 4.39 (d, 1H, $J_{1a,1b}$ 12.3 Hz, H-1a), 4.21 (d 2nd order, 1H, $J_{6b,5}$ 0-1 Hz, H-6b), 4.15 (m, 1H, H-5), 4.14 (d, 1H, $J_{1b,1a}$ 12.3 Hz, H-1b), 3.52 (m, 2H, $OC\underline{H}_2CH_2CH_2CH_3$), 2.10 (s, 12H, CH_3 acetyl), 1.53 (m, 2H, $OCH_2C\underline{H}_2CH_2CH_3$), 1.41 (m, 2H, $OCH_2CH_2C\underline{H}_2CH_3$) 0.95 (t, 3H, $OCH_2CH_2CH_2C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$, DEPT-135): δ 170.47, 170.01 (2x), 168.75 (C=O acetyl), 106.69 (C-2), 80.52, 79.48, 78.17 (C-3, C-4 and C-5), 63.23, 60.69, 58.82 (C-6, $O\underline{C}H_2CH_2CH_3$ and C-1), 31.58 ($OCH_2\underline{C}H_2CH_2CH_3$), 20.57 ($CH_3$ acetyl), 19.17 ($OCH_2CH_2\underline{C}H_2CH_3$), 13.67 ($OCH_2CH_2CH_2\underline{C}H_3$) ppm. Standard acetylation of the mixture of **26**, **28** and **30** yielded a mixture of the peracetates **27**, **29** and **31** (860 mg, 94%). GLC analysis: R_t 12.33 (**27**, 57%), R_t 12.39 (**29**, 14%) and R_t 12.61 (**31**, 29%). ^{13}C-NMR ($CDCl_3$): δ C-2 signals for **27**, **29** and **31** were observed at 106.62, 102.96 and 98.69 ppm respectively. A sample of the mixture of compounds **28** and **30** was crystallized from ethanol to afford pure **30**, m.p. 157-159^0 C, $[\alpha]_D$ -141.7^0 (c, 0.5, MeOH); lit.[17] m.p. 149-150^0 C, $[\alpha]_D$ -137.9^0; lit.[15] m.p. 156-158^0 C, $[\alpha]_D$ -145.2^0. Calculated for $C_{10}H_{20}O_6$ (236.27): C 50.84%, H 8.53%; Found: C 50.82%, H 8.48%. CI-MS: *m/z* 205 (M^+ - CH_2OH), 163 (M^+ - OC_4H_9), 145 (M^+ -

OC_4H_9 - H_2O). ^{1}H-NMR (D_2O): δ 3.94 (bs, 1H, H-3), 3.86 (bs, 2H, H-5 + H-4), 3.76 (d, 1H, $J_{6b,6a}$ 12.7 Hz, H-6b), 3.74 (s, 2H, H_{1a} + H_{1b}), 3.66 (dd, 1H, $J_{6a,6b}$ 12.7 Hz, $J_{6a,5}$ 1.7 Hz, H-6a), 3.46 (m, 2H, $OC\underline{H}_2CH_2CH_2CH_3$), 1.51 (m, 2H, $OCH_2C\underline{H}_2CH_2CH_3$), 1.31 (m, 2H, $OCH_2CH_2C\underline{H}_2CH_3$), 0.85 (t, 3H, $OCH_2CH_2CH_2C\underline{H}_3$) ppm. ^{13}C-NMR (DEPT-135, D_2O): δ 101.74 (C-2), 70.90, 70.42, 69.53 (C-3, C-4 and C-5), 65.06, 62.57, 62.09 ($O\underline{C}H_2CH_2CH_2CH_3$, C-6 and C-1), 32.63 ($OCH_2\underline{C}H_2CH_2CH_3$), 20.07 ($OCH_2CH_2\underline{C}H_2CH_3$), 14.48 ($OCH_2CH_2CH_2\underline{C}H_3$) ppm.

Reaction of D*-fructose* (**1**) *with 1-octanol in the presence of iodine.*

A stirred suspension of D-fructose (**1**, 2000 mg, 11.10 mmol) in methanol (100 ml) containing iodine (140 mg, 0.56 mmol, 0.05 equiv) was heated under reflux for 2 h and the clear, cooled reaction mixture was then concentrated *in vacuo*. The resultant syrup was dissolved in 1-octanol (100 ml) and set aside to stir at 50^0 C for 7 days. The mixture was decolourised with sodium thiosulphate, filtered and concentrated *in vacuo*. The crude material was dissolved in ethyl acetate, washed with saturated sodium hydrogen carbonate, dried (Na_2SO_4) and concentrated *in vacuo* to give a syrup. Column chromatography (1,2-dimethoxyethane / hexane, 3:1) of the crude product gave pure **32** (129 mg, 4%), and a mixture of compounds **32**, **34** and **36** (507 mg, 16%). Acetylation of the products in the usual manner gave the corresponding peracetates.

Compound **32** gave pure **33** (163 mg, 80%), $[\alpha]_D$ +54.4^0 ($CHCl_3$). GLC analysis: R_t 17.21 95%. ^{1}H-NMR ($CDCl_3$): δ 5.25 (d, 1H, H-3), 4.85 (dd, 1H, H-4), 4.40-3.99 (m, 5H, H-1ab, H-5, H6ab), 3.46 (m, 2H, H-1'), 2.10 (s, 12H, CH_3 acetyl), 1.21 (bs, 12H, alkyl chain), 0.82 (t, 3H, $O(CH_2)_7C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 170.42, 170.02 (2x), 168.73 (C=O acetyl), 106.73 (C-2), 80.54, 79.55, 78.23 (C-3, C-4 and C-5), 63.24, 61.07, 58.67 (C-6, $O\underline{C}H_2(CH_2)_6CH_3$ and C-1), 31.76, 29.57, 29.25, 29.22, 26.09, 22.56 (alkyl chain), 20.57 (CH_3 acetyl), 13.97 ($O(CH_2)_7\underline{C}H_3$) ppm. Compounds **32**, **34** and **36** yielded the mixture of the peracetates **33**, **35** and **37** (308 mg, 39%). GLC analysis: R_t 17.23 (**33** and **35**, 49%) and R_t 17.72 (**37**, 51%). ^{13}C-NMR ($CDCl_3$): δ C-2 signals for compounds **33**, **35** and **37** appeared at 106.70, 103.09 and 98.81 ppm, respectively

Reaction of 1-octanol in the presence of BF_3-methanolate with. -

(a) *D-Fructose* (**1**). A stirred suspension of D-fructose (**1**, 2000 mg, 11.10 mmol) in methanol (100 ml) containing iodine (140 mg, 0.56 mmol, 0.05 equiv) was heated under reflux for 2 h, whereon a clear solution was obtained. The cooled reaction mixture was concentrated *in vacuo* to approximately half of the volume and 1-octanol (40 ml) containing BF_3-methanolate (1 ml) was added. The reaction mixture was maintained at 40^{0}C for 1.5 h *in vacuo* (15 mm Hg). The mixture was treated with sodium thiosulphate until colourless, filtered and concentrated *in vacuo* to give a syrup. The crude material was dissolved in ethyl acetate (100 ml), washed with saturated aqueous sodium hydrogen carbonate (2 x 50 ml), and the organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a syrup. Column chromatography (dichloromethane / methanol, 9:1) of the crude product afforded a mixture of compounds **32** and **34** (496 mg, 15%), and a mixture of compounds **32**, **34** and **36** (774 mg, 24%). Acetylation of the mixtures with acetic anhydride and pyridine in the usual manner gave the corresponding peracetates.

The mixture of compounds **32** and **34** yielded a mixture of **33** and **35** (724 mg, 93%). GLC analysis: R_t 17.55 (**33** and **35**, 91%), R_t 4.21 (octylacetate, 7%). ^{13}C-NMR ($CDCl_3$): δ C-2 signals for **33**, and **35** were observed at 106.67 and 103.24 ppm, respectively. The mixture of compounds **32**, **34** and **36** yielded **33**, **35** and **37** (1159 mg, 95%). GLC analysis: R_t 17.44 (**33** and **35**, 89%) and Rt 17.83 (**37**, 11%). ^{13}C-NMR ($CDCl_3$): δ C-2 signals for compounds **33**, **35** and **37** were observed at 106.66, 103.05 and 98.76 ppm, respectively

(b) *Inulin* (**3**). A stirred suspension of inulin (**3**, 2000 mg, 11.10 mmol) in methanol (100 ml) containing iodine (140 mg, 0.56 mmol, 0.05 equiv) was heated under reflux for 3 h, whereon a clear solution was obtained. The cooled reaction mixture was concentrated *in vacuo* to approximately half of the volume and 1-octanol (40 ml) containing BF_3-methanolate (1 ml) was added. The reaction mixture was maintained at 40^{0}C for 1.5 h *in vacuo* (15 mm Hg), cooled and then treated with sodium thiosulphate until colourless, filtered and concentrated *in vacuo* to give a syrup. The crude material was dissolved in ethyl acetate (100 ml), washed with saturated aqueous sodium hydrogen carbonate (2 x 50 ml), and the organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a syrup. Flash column chromatography (dichloromethane / methanol, 9:1) of the crude material afforded pure compound **32** (196 mg, 6%), a mixture of compounds **32** and **34** (466 mg, 14%), and then pure compound **34** (175 mg, 5%). Acetylation of the various products with acetic anhydride and pyridine in the usual manner afforded the corresponding peracetates.

Compound **32** gave **33** (284 mg, 92%). GLC analysis: R_t 17.29 min 94%. $[\alpha]_D$ +61.5^0 ($CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 5.32 (d, 1H, $J_{3,4}$ 1.4 Hz, H-3), 4.91 (dd, 1H, $J_{4,5}$ 4.5 Hz, H-4), 4.43 (dd, 1H, $J_{6a,6b}$ 10.9 Hz, $J_{6a,5}$ 3.1 Hz, H-6a), 4.40 (d, 1H, $J_{1a,1b}$ 12.3 Hz, H-1a), 4.19 (d 2nd order, 1H, $J_{6b,5}$ 0-1 Hz, H-6b), 4.18 (m, 1H, H-5), 4.13 (d, 1H, $J_{1b,1a}$ 12.3 Hz, H-1b), 3.52 (m, 2H, $OC\underline{H}_2(CH_2)_6CH_3$), 2.10 (s, 12H, CH_3 acetyl), 1.54 (m, 2H, $OCH_2C\underline{H}_2(CH_2)_5CH_3$), 1.28 (m, 10H, alkyl chain) 0.88 (t, 3H, $O(CH_2)_7C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$, DEPT-135): δ 170.47, 170.04 (2x), 168.75 (C=O acetyl), 106.70 (C-2), 80.52, 79.48, 78.20 (C-3, C-4 and C-5), 63.23, 61.05, 58.82 (C-6, $O\underline{C}H_2(CH_2)_6CH_3$ and C-1), 31.75 ($OCH_2\underline{C}H_2(CH_2)_5CH_3$), 29.54, 29.23, 26.07, 22.55 (alkyl chain), 20.59 (CH_3 acetyl), 13.98 ($O(CH_2)_7\underline{C}H_3$) ppm. Acetylation of compound **34** yielded **35** (251 mg, 91%). GLC analysis: R_t 17.32 100%. $[\alpha]_D$ -23.2^0 ($CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 5.44 (d, 1H, $J_{3,4}$ 6.3 Hz, H-3), 5.38 (dd, 1H, $J_{4,5}$ 5.8 Hz, H-4), 4.32 (dd, 1H, $J_{6a,6b}$ 11.0 Hz, $J_{6a,5}$ 3.1 Hz, H-6a), 4.28 (d, 1H, $J_{1a,1b}$ 11.8 Hz, H-1a), 4.20 (d 2nd order, 1H, $J_{6b,5}$ 0-1 Hz, H-6b), 4.15 (m, 1H, H-5), 4.14 (d, 1H, $J_{1b,1a}$ 11.8 Hz, H-1b), 3.57 (m, 2H, $OC\underline{H}_2(CH_2)_6CH_3$), 2.10 (s, 12H, CH_3 acetyl), 1.55 (m, 2H, $OCH_2C\underline{H}_2(CH_2)_5CH_3$), 1.29 (m, 10H, alkyl chain) 0.88 (t, 3H, $O(CH_2)_7C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$, DEPT-135): δ 170.44, 170.06 (2x), 169.85 (C=O acetyl), 103.09 (C-2), 77.89, 76.38, 75.97 (C-3, C-4 and C-5), 64.27, 63.07, 62.36 (C-6, $O\underline{C}H_2(CH_2)_6CH_3$ and C-1), 31.73 ($OCH_2\underline{C}H_2(CH_2)_5CH_3$), 29.77, 29.20, 29.17, 25.98, 22.56 (alkyl chain), 20.59 (CH_3 acetyl), 14.01 ($O(CH_2)_7\underline{C}H_3$) ppm.

Reaction of sucrose (**2**) *with methanol containing iodine.*

A stirred suspension of sucrose (**2**, 1000 mg) in methanol (50 ml) containing iodine (70 mg, 0.28

mmol, 0.05 equiv) was heated under reflux for 16 h and the resulting clear solution was processed as described above. The crude material was acetylated with pyridine (10 ml) and acetic anhydride (5 ml) in the usual manner to afford 2203 mg (77%) of a mixture of compounds **5**, **7**, **9** (fructosides) and **48**, **50**, **52**, **54** (glucosides) as a syrup. ^{13}C-NMR ($CDCl_3$): δ C-2 signals for compounds **50**, **5**, **7**, **54**, **48**, **9** and **52** were detected at 107.44, 106.77, 102.63, 101.45, 101.03, 98.74 and 96.66 ppm, respectively.

Reaction of D-*glucose* (**44**) *with methanol containing iodine.* -

(a) *With 0.05 equiv.* A stirred suspension of D-glucose (**44**, 2000 mg, 11.10 mmol) in methanol (100 ml) was treated with iodine (140 mg, 0.55 mmol, 0.05 equiv) and the mixture was heated under reflux for 40 h, whereon a clear solution was obtained. The cooled mixture was treated with solid sodium thiosulphate until colourless, filtered and concentrated *in vacuo* to give a colourless syrup. Column chromatography (dichloromethane / methanol, 9:1) of the crude product (2.5 g) afforded a mixture of compounds **47** and **49** (1424 mg, 66%). ^{13}C-NMR (D_2O)): δ C-1 signals for compounds **47** and **49** were observed at 103.03 and 108.95 ppm, respectively.

Treatment of the mixture of **47** and **49** under standard conditions of acetylation with acetic anhydride and pyridine afforded a mixture of the corresponding peracetates **48** and **50** (2417 mg, 91%) as a colourless syrup. GLC analysis: R_t 11.05 (**48**, 50%), R_t 11.20 (**50**, 50%). ^{1}H-NMR ($CDCl_3$): δ 5.55, 5.49 (2d, 1H, H-3), 4.45-4.0 (m, 5H glucose skeleton, unresolved), 4.15 (dd, 1H, H-6'), 3.41, 3.39 (2s, 3H, OCH_3), 2.10 (s, 12H, CH_3 acetyl) ppm. ^{13}C-NMR ($CDCl_3$): δ C-1 signals for compounds **48** and **50** detected at 101.11 and 107.52 ppm, respectively.

In another experiment a stirred suspension of D-glucose (**44**, 2000 mg, 11.10 mmol) in methanol (100 ml) containing iodine (140 mg, 0.55 mmol, 0.05 equiv) was heated under reflux for 40 h and then processed as described above in (a). The crude reaction mixture was not purified but acetylated directly with pyridine (12 ml) and acetic anhydride (8 ml) in the usual manner to afford a mixture of compounds **48**, **50**, **52** and **54** (3868 mg, 96%) as a syrup. GLC analysis: R_t 11.07 (**48**, 31%), R_t 11.24 (**50**, 48%), R_t 11.38 (**52**, 3%), R_t 11.45 (**54**, 4%), R_t 12.41 (**55** and **56**, 14%). ^{13}C-NMR ($CDCl_3$): δ C-1 signals for compounds **48**, **50**, **52** and **54** were detected at 100.85, 107.25, 96.52 and 101.34 ppm, respectively, and for the by-products **55** and **56** at 88.77 and 91.38 ppm, respectively. (In a reference ^{13}C-NMR spectrum of compounds **55** and **56** their C-1 resonances appeared at 88.85 and 91.49 ppm, respectively).

In another experiment, treatment of D-glucose (**44**, 2000 mg, 11.10 mmol) with iodine (140 mg, 0.55 mmol, 0.05 equiv) in the same manner, but for 64 h gave again a mixture of compounds **48**, **50**, **52** and **54** (3841 mg, 95%) as a syrup. GLC analysis: R_t 11.17 (**48**, 32%), R_t 11.35 (**50**, 50%), R_t 11.48 (**52**, 7%), R_t 11.55 (**54**, 6%), R_t 12.48 (**55** and **56**, 5%).

(b) *With 0.10 equiv.* A stirred suspension of D-glucose (**44**, 2000 mg, 11.10 mmol) in methanol (100 ml) was treated with iodine (280 mg, 1.10 mmol, 0.10 equiv) and the mixture was heated under reflux for 30 h and the resulting clear solution processed as described above in (a). The crude reaction mixture (2.5 g) was acetylated with pyridine (10 ml) and acetic anhydride (6 ml) in

the usual manner to afford a mixture of compounds **48**, **50**, **52** and **54** (3452 mg, 86%) as a syrup. GLC analysis: R_t 11.10 (**48**, 34%), R_t 11.28 (**50**, 56%), R_t 11.39 (**52**, 4%), R_t 11.46 (**54**, 5%), R_t 12.44 (**55** and **56**, 1%). ^{13}C-NMR ($CDCl_3$): δ C-1 signals for compounds **48**, **50**, **52** and **54** were detected at 101.03, 107.44, 96.97 and 101.60 ppm, respectively.

In another experiment, treatment of D-glucose (**44**, 2000 mg, 11.10 mmol) with iodine (140 mg, 0.55 mmol, 0.05 equiv) in the same manner, but for 64 h gave essentially the same result. GLC analysis: R_t 11.22 (**48**, 29%), R_t 11.40 (**50**, 46%), R_t 11.54 (**52**, 11%), R_t 11.62 (**54**, 10%), R_t 12.54 (**55** and **56**, 4%).

D-Glucose diethyl dithioacetal (**57**). A solution of D-glucose (**44**, 10g, 55.5 mmol) in hydrochloric acid (concentrated, 9 ml) was treated with ethanethiol (10 ml) as described[34], to afford crystalline **57** (10.3 g, 65%); m.p. 127°C (from water), lit.[34] 127°C.

Penta-O-*acetyl-D-glucose diethyl dithioacetal* (**58**). A cooled (0°C) solution of compound **57** (10.3 g, 36.0 mmol) in pyridine (75 ml) was treated with acetic anhydride (75 ml) as described[34], to yield, after processing, compound **58** as an oil (11.0 g, 61%) which crystallized slowly from water; m.p. 42-44°C, $[\alpha]_D$ +11° ($CHCl_3$), lit.[34] m.p. 45-47°C, $[\alpha]_D$ +11°. GLC-analysis: R_t 11.28 (97%). ^{1}H-NMR ($CDCl_3$): δ 5.75 (dd, 1H, H-3), 5.5-5.0 (m, 4H, H-1, H-2, H-4, H-5), 4.2-4.0 (m, 2H, H-$6_{a,b}$), 2.9-2.4 (m, 4H, S$\underline{CH_2}$$CH_3$), 2.1 (5s, 15H, CH_3 acetyl), 1.6-1.1 (m, 6H, $SCH_2C\underline{H_3}$) ppm.

Penta-O-*acetyl*-aldehydo-*D-glucose* (**59**). A solution of the acetate **58** (1.28 g, 2.6 mmol) in acetone (3 ml) was added to a stirred cooled (0°C) solution of *N*-bromosuccinimide in water / acetone[35] (25 ml, 3:97 v/v), and after 3 min 2.0 g of $NaHCO_3$ / $Na_2S_2O_3$ (1/1) was added. After 3 h of additional stirring the solid material was removed by filtration, washed with acetone and the combined filtrate and washings concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (75 ml), washed with water, dried ($MgSO_4$/$NaHCO_3$), concentrated *in vacuo*, and the crude oily product crystallized (acetone / hexane) to afford crystalline **59** (0.47 g, 47%, lit.[35] 33%); m.p. 118-119°C, lit.[35] m.p. 116-117°C. ^{1}H-NMR ($CDCl_3$): δ 9.5 (s, 1H, H-1), 5.7-5.0 (m, 4H, H-2, H-3, H-4, H-5), 4.2-4.0 (m, 2H, H-$6_{a,b}$), 2.1 (5s, 15H, CH_3 acetyl) ppm.

Penta-O-*acetyl-D-glucose dimethyl acetal* (**60**). A solution of compound **59** (250 mg, 0.64 mmol) in 2,2-dimethoxypropane (2 ml) and CH_2Cl_2 (2 ml) was treated with *p*-toluenesulphonic acid (2 mg) at room temperature[36] for 4 days. The reaction mixture was then neutralised with solid $NaHCO_3$, filtered, the organic layer washed successively with water and aqueous saturated $NaHCO_3$, dried ($MgSO_4$/$NaHCO_3$) and concentrated *in vacuo* to give a solid residue (279 mg). Column chromatography (acetone / hexane, 1:3) of the crude material followed by crystallization (diethyl ether / heptane) afforded crystalline **60** (102 mg, 39%); m.p. 70-71°C, $[\alpha]_D$ +12° ($CHCl_3$), lit.[34] m.p. 71-72°C, $[\alpha]_D$ +12°. GLC-analysis: R_t 9.81 (100%). ^{1}H-NMR ($CDCl_3$): δ 5.50 (t, 1H, H-2), 5.40 (t, 1H, $J_{3,4}$ 5.3 Hz, H-3), 5.17 (t, 1H, H-4), 5.10 (m, 1H, H-5), 4.35 (d, 1H, $J_{1,2}$ 5.5 Hz, H-1), 4.29 (dd, 1H, $J_{6a,5}$ 4.0 Hz, $J_{6a,6b}$ 12.2 Hz, H-6a), 4.10 (dd, 1H, $J_{6b,5}$ 6.0 Hz, H-6b), 3.40 (s, 3H, OMe), 3.36 (s, 3H, OMe), 2.10 (s, 15H, CH_3 acetyl) ppm. ^{13}C-NMR {H} ($CDCl_3$): δ 170.47, 169.91, 169.80 (2X), 169.51 (C=O acetyl), 102.39 (C-1), 69.82, 69.35, 69.89, 68.69 (C-2, C-3, C-4 and C-5), 61.67 (C-6),

56.10, 53.75 (OCH_3), 20.6 (CH_3 acetyl) ppm.

D-Glucose dimethyl acetal (**61**). A solution of the acetate **60** (90 mg, 0.21 mmol) in methanol (5 ml) was treated with potassium cyanide[37] (1.6 mg) and stirred at room temperature for 4 h. The mixture was filtered through a layer of silica gel (60H) and the filtrate concentrated *in vacuo* to afford **61** (49 mg, 100%) as an colourless oil. The product was used immediately in the next step. TLC-analysis: R_f 0.23 (Solvent A).

Reaction of D-glucose dimethyl acetal (**61**) *with methanol containing iodine.* A stirred solution of the acetal **61** (49 mg, 0.22 mg) in methanol (2 ml) containing iodine (6 mg, 0.02 mmol, 0.11 equiv) was heated under reflux for 40 h and the resulting clear solution was processed as described above in (a). The crude material was acetylated with pyridine (1 ml) and acetic anhydride (1 ml) in the usual manner to afford 65 mg (82%) of a mixture of the methyl D-glucofuranosides **48** and **50** together with compound **60** as a syrup. GLC analysis: R_t 11.10 (**48**, 36%), R_t 11.25 (**50**, 56%), R_t 12.46 (**60**, 7%), R_t 12.48 (**55** and **56**, 0.5%). ^{13}C-NMR (IGDE, $CDCl_3$): δ C-1 signals for compounds **48**, **50** and **60** were detected at 101.08, 107.49 and 102.60 ppm, respectively, and for compounds **55** and **56** at 88.9 and 91.7 ppm, respectively. From the the integration of the C-1 signals in the IGDE[38] (T_1= 25 s) ^{13}C-NMR spectrum the ratio of compounds **48** and **50** was calculated to be 57:40.

In another experiment treatment of **61** with iodine (0.06 equiv) in the same manner, but for 29 h, gave a mixture of compounds **60** and **48** and **50**. GLC analysis: R_t 11.13 (**48**, 2%), R_t 11.28 (**50**, 3%), R_t 12.49 (**60**, 95%).

5.6 References and notes

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IODINE-CATALYZED SYNTHESIS OF ALKYL D-GLUCOSIDES

6.1 Introduction

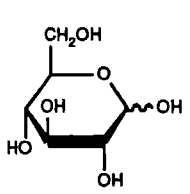
The synthesis of several alkyl glycosides from D-fructose, sucrose and inulin was described in Chapter 5. It was demonstrated that iodine can be used as an effective catalyst for the direct glycosidation of D-fructose with various alcohols which lead to product mixtures of alkyl D-fructosides wherein the alkyl D-fructofuranosides clearly preponderated. The procedures used were simple and in most cases the pure α-D-fructofuranosides could be readily isolated from the product mixtures by column chromatography. In section 5.3 the direct iodine-catalyzed methanolysis of D-glucose (**1**) leading to mixtures of methyl D-glucosides was described. The methyl D-glucofuranosides were also preponderant in these reactions.

It has already been demonstrated[1] that various acetals can be cleaved by dilute solutions of iodine in methanol. Benzylidene, ethylidene and isopropylidene acetals are cleaved at room temperature, or by heating under reflux for short periods. Derivatives having a free hydroxyl group at the anomeric centre are converted into mixtures composed mainly of methyl glycofuranosides if the reaction mixtures were heated under reflux for prolonged periods. Methanolysis of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) with iodine catalysis (0.5% w/v) in this way afforded a product mixture with the methyl D-glucofuranosides as the main products (70%), together with a small amount of methyl D-glucopyranosides (10%)[1]. The use of higher alcohols in these reactions was not reported.

When the direct iodine-catalyzed glycosidation of D-glucose (**1**) was attempted with ethanol and 1-butanol analysis (TLC) indicated that no reaction had occurred, and that **1** remained essentially undissolved. In view of this lack of reactivity it was decided to investigate the reaction of the diacetal **2** with higher alcohols in the presence of iodine because of its greater solubility. In this chapter the transglycosidation of the methanolysis products of **2** with higher alcohols in the presence of iodine is also described.

6.2 Results and discussion

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**2**) is a well known derivative of D-glucose. There are a number[2,3] of well-established syntheses of **2**, using conventional acid catalysts. An improved method for the synthesis of **2** using iodine catalysis is described[4] in Chapter 3.



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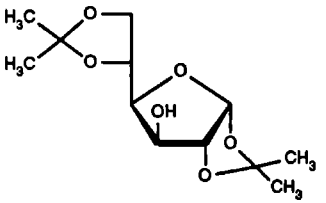

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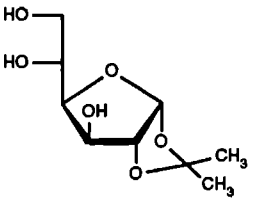

3

Thus, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) was treated with various alcohols in the presence of catalytic amounts of iodine by the same method as described in Chapter 5. The excesses of the alcohols remaining at the end of the reactions could be recovered by distillation *in vacuo* for further use in subsequent reactions, thereby increasing the efficiency and reducing the costs of the procedure. The reaction conditions and the results obtained are depicted in Table 1.

Scheme 1

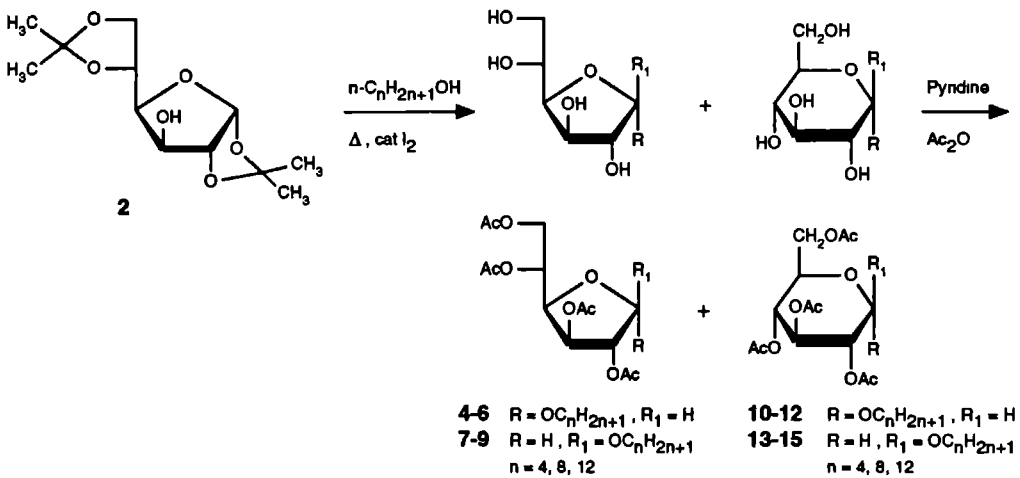

Table 1 Glycosidation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (2).

entry	n-$C_nH_{2n+1}OH$	equiv I_2	conditions	product(s) #	yield
1	n = 4	0.05	17 h, RT	- *	- *
2	n = 4	0.52 [b]	19 h, reflux	**10** **13**	50% [a] 20% [a]
3	n = 8	0.05	27 h, 75°C	- *	- *
4	n = 12	0.52 [b]	7 d, 130°C	**12** **15**	28% [c] 09% [c]

a) after column chromatography b) conditions ref. 1. c) determined from crude reaction mixture by GLC-analysis.
*) only starting material was isolated #) after acetylation.

When **2** was treated with 0.05 equivalents of iodine, in 1-butanol at room temperature for 17 h (entry 1) under the conditions described (see also Chapter 5), only unreacted **2** was isolated. When the reaction mixture was heated under reflux unreacted material **2** (20%), and the corresponding 1,2-*O*-isopropylidene monoacetal **3** (73%) were the only products isolated. These conditions were apparently insufficient to cause glycosidation, and only partial hydrolysis of the acetal **2** had occurred. It was then shown that under more forcing conditions, *i.e.* with 0.52 equivalents of iodine (0.5% w/v)[1], glycosidation of **2** was possible. Thus, treatment of **2** with boiling 1-butanol in the presence of iodine (0.52 equiv) for 19 h (entry 2), followed by subsequent acetylation, afforded a mixture of acetylated butyl D-glucopyranosides **10** and **13**, which were isolated by column chromatography in 50 and 20% yields, respectively.

Treatment of **2** with 1-octanol under moderate conditions (0.05 equivalents of iodine, entry 3) did not, as expected, cause glycosidation and only starting material **2** was isolated. Treatment of **2** with 1-dodecanol and 0.52 equivalents of iodine at 130^{0}C for 7 days (entry 4), followed by acetylation, however, yielded a mixture of glycosides. Analysis (GLC, NMR) indicated the presence of the peracetates of dodecyl α-D-glucopyranoside **12** (28%) and dodecyl β-D-glucopyranoside **15** (9%).

From these experiments it was concluded that the diacetal **2** could be used in iodine-catalyzed glycosidation reactions with higher alcohols for the synthesis of alkyl glucosides, but that concentrations of iodine higher than used previously in the acetal deprotection method[1], *i.e.* 0.5% (w/v), were required. Only alkyl D-glucopyranosides were obtained probably as a result of the more forcing conditions used in the procedure.

An alternative approach to the synthesis of alkyl glucosides is the use of the previously described[1] iodine-catalyzed methanolysis product of the diacetal **2**, which is a mixture of methyl D-glucosides, in transglycosidation reactions with higher alcohols also catalyzed by iodine. It has been demonstrated (Chapter 5) that low concentrations of iodine (0.05 equiv, 0.14% w/v), rather than the higher concentrations (0.5% w/v) of iodine, used in the acetal deprotection method[1], were sufficient to cause glycosidation. The mixture of methyl D-glucosides is obtained more readily from **2** than from the direct methanolysis of D-glucose (**1**) (Chapter 5), and requires shorter reaction times because of the higher solubility of **2** in methanol.

In the following experiments 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) was treated with boiling methanol in the presence of iodine (0.05 equiv) for 24 h, as described earlier, to yield a mixture of methyl D-glucosides. The chosen higher alcohol was then added to the mixture and the remaining excess of methanol removed *in vacuo* under carefully controlled conditions. The transglycosidation reaction was then performed by heating the reaction mixture at the optimum temperatures. The excesses of the higher alcohols used in the reactions could be recovered by distillation *in vacuo* for further use in subsequent reactions. The reaction conditions and the results obtained are listed in Table 2.

Scheme 2

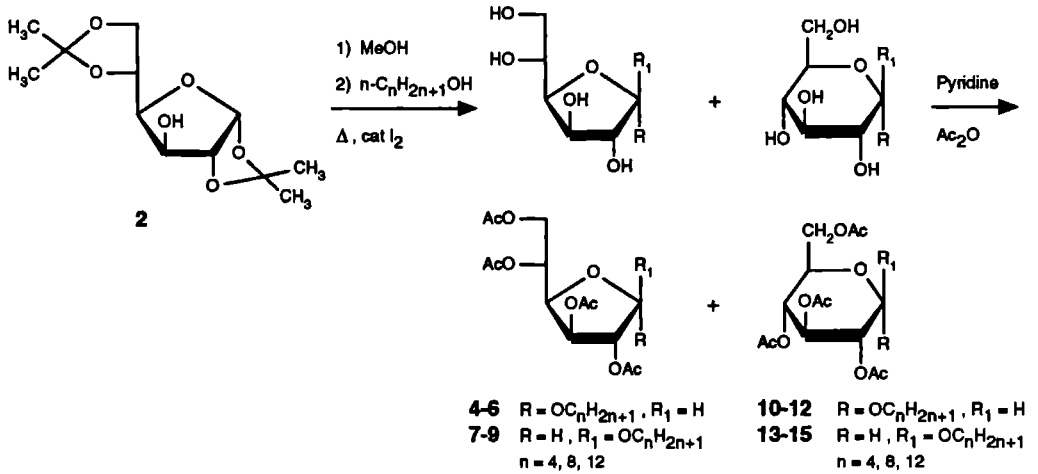

Table 2 Transglycosidation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (2).

entry	n-$C_nH_{2n+1}OH$	equiv I_2	conditions	product(s) #	yield
1	n = 4	0.05	4 d, 70°C + 4 d, reflux	10 13	5% a 22% a
2	n = 4	0.05	4 d, reflux	4 7	15% a 15% a
3	n = 8	0.05 0.52 b	8 d, 100°C + 1 d, 100°C	8 11 14	1% a 10% a 6% a
4	n = 8	0.05	10 d, 110°C	5 8 11 14	21% c 15% c 23% c 24% c
5	n = 12	0.52 b	6 d, 90°C + 7 d, 130°C	12 15	20% a 4% a
6	n = 12	0.05	6 d, 100°C	6 9 12 15	13% c 19% c 14% c 15% c

a) after column chromatography. b) conditions ref. 1. c) determined from crude reaction mixture by GLC-analysis. #) after acetylation.

Treatment of the mixture of methyl D-glucosides obtained by the iodine-catalyzed (0.05 equiv) methanolysis of **2**, with 1-butanol (still containing 0.05 equivalents of iodine) at 70°C for 4 days and then under reflux for 4 days (entry 1), with subsequent acetylation, afforded the acetylated butyl D-glucopyranosides **10** and **13**. These were isolated by column chromatography in yields of 5

and 22%, respectively. When the reaction mixture was heated under reflux from the beginning of the transglycosidation process for 4 days (entry 2), analysis (GLC) of the acetylated product mixture indicated the presence of the peracetates of butyl α-D-glucofuranoside (**4**) and the butyl β-D-glucofuranoside (**7**), which were isolated by column chromatography, both in yields of 15%. A small amount (6%) of unreacted acetylated methyl D-glucosides was also isolated from the reaction mixture. These conditions seem to favour the production of either of the thermodynamically controlled pyranosides (entry 1), or the kinetic derived furanoside products (entry 2).

Treatment of the mixture of methyl D-glucosides derived from **2** with 1-octanol at 100^{0}C for 8 d in the presence of 0.05 equivalents of iodine and then with 0.52 equivalents of iodine[1] for 1 day at the same temperature (entry 3), with subsequent acetylation, gave the acetylated octyl β-D-glucofuranoside (**8**), and the octyl D-glucopyranosides **11** and **14**, which were obtained by column chromatography in yields of 1, 10 and 6%, respectively. It was then demonstrated that under less forcing conditions, *i.e.* with 0.05 equivalents of iodine, but with longer reaction times (10 days, entry 4) relatively more of the kinetically controlled furanoside products were formed. Analysis (GLC, NMR) of the product mixture obtained after acetylation showed the presence of all four possible glycosides which were identified as a mixture of the peracetates of octyl α-D-glucofuranoside **5** (21%), octyl β-D-glucofuranoside **8** (15%), octyl α-D-glucopyranosides **11** (23%) and octyl β-D-glucopyranosides **14** (24%).

When the same mixture of methyl D-glucosides was treated with 1-dodecanol in the presence of 0.52 equivalents of iodine (0.5% w/v)[1] under more forcing conditions (6 d, 90^{0}C and then 7 days, 130^{0}C, entry 5), followed by subsequent acetylation, the acetylated dodecyl D-glucopyranosides **12** and **15**, were isolated by column chromatography in yields of 20 and 4%, respectively. When the reaction with 1-dodecanol was performed under more moderate conditions, *i.e.* with 0.05 equivalents of iodine at 100^{0}C for 6 days (entry 6), it was then shown that relatively more of the kinetically controlled furanoside products were produced. Analysis of the acetylated product mixture indicated the presence of four glycosides which were identified as a mixture of the peracetates dodecyl α-D-glucofuranoside **6** (13%), dodecyl β-D-glucofuranoside **9** (19%), dodecyl α-D-glucopyranosides **12** (14%) and dodecyl β-D-glucopyranoside **15** (15%).

It can be concluded from these results that the diacetal **2** can also be used in the indirect synthesis of alkyl D-glucosides in an iodine-catalyzed transglycosidation process but that in general longer reaction times at elevated temperatures were required, and that the desired products are obtained in only moderate yields.

Despite the use of low catalytic amounts of iodine only mixtures of glycosides can be obtained from **2** using either the direct or the transglycosidation procedure. This is in contrast to the direct iodine-catalyzed glycosidations of D-fructose (Chapter 5) where the furanosides were clearly preponderant in the reaction mixtures and they could be isolated easily by chromatography. The use of more forcing conditions, *i.e.* with higher amounts of iodine (0.5% w/v), leads only to the synthesis of the more thermodynamically favoured D-glucopyranosides.

6.3 Experimental

General methods

Optical rotations were determined with a Perkin-Elmer automatic polarimeter, model 241 MC on 1% solutions at 20°C. Thin-layer chromatography (TLC) on pre-coated plates of silica gel (Merck) was performed with dichloromethane - methanol (4/1, v/v, solvent A) or hexane - ethyl acetate (1/1, v/v, solvent B). Detection was affected by spraying with 3% H_2SO_4 in ethanol followed by heating at 140°C. GLC was performed with a Hewlett-Packard 5790 or 5890 series II gaschromatograph using a fused silica capillary column (25m) coated with HP-1 cross-linked methyl silicone gumphase or a capillar column (25m) of medium polarity (PAS 1701) operating at 100-150°C; 100°C (isothermally, 5 min) followed by 5°C/min for 10 min; or a temperature programme from 100-250°C at 15°C/min, followed by 10 min at 250°C (isothermal), with nitrogen as the carrier gas (2 ml/min). Compounds were identified by co-injection with authentic samples and the percentages composition of the analysed mixtures are all relative. Melting points were determined on a Reichert thermopan microscope and are uncorrected. ^{1}H-NMR spectra were recorded with a Bruker AC 100 (100 MHz) or Bruker AM 400 (400 MHz) spectrometer on solutions in $CDCl_3$ (internal standard Me_4Si). ^{13}C-NMR spectra were recorded with a Bruker AC 100 or Bruker AM 400 spectrometer operating at 25 and 100.6 MHz, respectively, on solutions in $CDCl_3$ (internal Me_4Si). Pyridine was distilled from potassium hydroxide and hexane from calcium hydride, before use.

Butyl α-D-glucopyranoside (**10**) *and butyl β-D-glucopyranoside* (**13**) *(Table 1, entry 2).* A stirred suspension of **2** (500 mg, 1.92 mmol) in 1-butanol (50 ml) was treated with iodine (250 mg, 0.98 mmol, 0.52 equiv) and the mixture heated under reflux for 19 h, whereon a clear solution was obtained. The cooled mixture was treated with 0.5 M aqueous sodium thiosulphate solution until colourless and the organic layer concentrated *in vacuo*. The resulting crude product mixture was acetylated in the usual manner (pyridine and acetic anhydride). GLC-analysis: R_t 9.82 (**10**, 66%), 9.96 (**13**, 28%). Column chromatography (hexane/ethyl acetate, 3:1) of the crude material afforded **10** as a colourless oil (380 mg, 50%), $[\alpha]_D$ +138.7° (H_2O); lit.[5] $[\alpha]_D$ +135.4°. ^{1}H-NMR ($CDCl_3$): δ 5.47 (d, 1H, H-3), 5.2-4.7 (m, 3H, H-1, H-2, H-4), 4.4-3.9 (m, 3H, H-5, H-6ab), 3.6-3.3 (m, 2H, $OC\underline{H}_2(CH_2)_2CH_3$), 2.1 (4s, 12H, CH_3 acetyl), 1.7-1.2 (m, 4H, $OCH_2(C\underline{H}_2)_2CH_3$), 0.95 (t, 3H, $OCH_2(CH_2)_2C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 170.30, 169.87, 169.62, 169.00 (C=O acetyl), 95.42 (C-1), 70.72, 70.02, 68.46, 66.97 (C-2, C-3, C-4, C-5)[7], 61.78 (C-6), 68.14 ($O\underline{C}H_2(CH_2)_2CH_3$), 31.08 ($OCH_2\underline{C}H_2CH_2CH_3$), 19.01 ($OCH_2CH_2\underline{C}H_2CH_3$), 13.52 ($OCH_2CH_2CH_2\underline{C}H_3$), 20.4 ($CH_3$ acetyl) ppm. Further elution gave compound **13** (154 mg, 20%) as a white solid which on recrystallization (hexane) gave pure **13**, m.p. 63-65°C, $[\alpha]_D$ -25.4° (EtOH); lit.[5] m.p. 65-66°C, $[\alpha]_D$ -26.8°. ^{1}H-NMR ($CDCl_3$): δ 5.21 (t, 1H, $J_{3,4}$ 9.5 Hz, H-3), 5.09 (t, 1H, $J_{4,5}$ 9.7 Hz, H-4), 4.98 (t, 1H, $J_{2,3}$ 9.2 Hz, H-2), 4.49 (d, 1H, $J_{1,2}$ 8.0 Hz, H-1), 4.26 (dd, 1H, $J_{6a,6b}$ 12.3 Hz, $J_{6a,5}$ 4.7 Hz, H-6a), 4.13 (dd, 1H, $J_{6b,5}$ 2.3 Hz, H-6b), 3.88 (m, 2H, $OC\underline{H}_2(CH_2)_2CH_3$), 3.68 (m, 1H, H-5), 3.48 (m, 2H, $OC\underline{H}_2(CH_2)_2CH_3$), 2.1

(4s, 12H, CH_3 acetyl), 1.56 (m, 2H, $OCH_2\underline{CH_2}CH_2CH_3$), 1.35 (m, 2H, $OCH_2CH_2\underline{CH_2}CH_3$), 0.90 (t, 3H, $OCH_2CH_2CH_2\underline{CH_3}$) ppm. ^{13}C-NMR ($CDCl_3$): δ 170.67, 170.30, 169.39, 169.28 (C=O acetyl), 100.83 (C-1), 71.35, 72.86, 68.50, 71.72, (C-3, C-5, C-2, C-4)[7], 62.00 (C-6), 69.89 ($O\underline{CH_2}(CH_2)_2CH_3$), 31.37 ($OCH_2\underline{CH_2}CH_2CH_3$), 18.93 ($OCH_2CH_2\underline{CH_2}CH_3$), 13.68 ($OCH_2CH_2CH_2\underline{CH_3}$), 20.4 ($CH_3$ acetyl) ppm.

Dodecyl α-D-glucopyranoside (**12**) *and dodecyl β-D-glucopyranoside* (**15**) *(Table 1, entry 4).* A stirred suspension of **2** (500 mg, 1.92 mmol) in 1-dodecanol (50 ml) was treated with iodine (250 mg, 0.98 mmol, 0.52 equiv) and the mixture heated at 130^{0}C for 7 days. The mixture was concentrated *in vacuo* (0.5 mm Hg) to remove the excess of 1-dodecanol, and was then processed and acetylated as described above. Column chromatography (hexane/ethyl acetate, 3:1) of the crude material yielded a mixture of the peracetates **12** and **15** as a colourless oil (366 mg, 37%). GLC-analysis[6]: R_t 10.18 (**12**, 75%), 10.47 (**15**, 25%). ^{13}C-NMR ($CDCl_3$): characteristic C-1 signals for compounds **12** and **15** were observed at δ 95.51 and 100.71 ppm, respectively.

Reaction of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**2**) *with methanol followed by transglycosidation with :*

(a) *1-butanol (Table 2, entry 1).* A solution of **2** (500 mg, 1.92 mmol) in methanol (50 ml) was treated with iodine (25 mg, 0.10 mmol, 0.05 equiv) and the mixture heated under reflux for 24 h. 1-Butanol (50 ml) was then added and the mixture concentrated carefully *in vacuo* to approximately half of the volume to remove the excess of methanol. The resulting mixture was maintained at 70^{0}C for 4 days followed by heating under reflux for 4 days. The cooled solution was treated with 0.5 M aqueous sodium thiosulphate solution until colourless and the organic layer was concentrated *in vacuo*. The resulting material was acetylated in the usual manner (pyridine and acetic anhydride). GLC-analysis: R_t 9.31 (**10**, 19%), 9.82 (**13**, 79%). Column chromatography (hexane/ethyl acetate, 3:1) of the mixture afforded compound **10** as a colourless oil (37 mg, 5%). GLC-analysis: R_t 9.42 (98%). Further elution gave compound **13** (173 mg, 22%) also as an colourless oil. GLC-analysis: R_t 9.71 (99%). The ^{1}H-NMR and ^{13}C-NMR spectra of the products **10** and **13** were identical to those described above.

(b) *1-butanol (Table 2, entry 2).* A stirred solution of **2** (500 mg, 1.92 mmol) was treated with methanol and iodine as described in (a), exept that the mixture was heated under reflux for 4 days, and processed and acetylated as described above in (a). Column chromatography (hexane/ethyl acetate, 3:1) of the crude product mixture afforded a small amount of methyl D-glucosides (44 mg), and then compound **4** as a colourless oil (112 mg, 15%). GLC-analysis: R_t 9.12 (97%). $[\alpha]_D$ -32.5^0 (EtOH). ^{1}H-NMR ($CDCl_3$): δ 5.34 (d, 1H, H-1), 5,25 (m, 1H, H-5), 5.0 (s, 2H, H-2, H-3), 4.6-4.4 (m, 2H, H-4, H-6a), 4.12 (dd, 1H, H-6b), 3.9-3.3 (m, 2H, $O\underline{CH_2}(CH_2)_2CH_3$), 2.1 (4s, 12H, CH_3 acetyl), 1.7-1.3 (m, 4H, $OCH_2(\underline{CH_2})_2CH_3$), 0.93 (t, 3H, $OCH_2(CH_2)_2\underline{CH_3}$) ppm. ^{13}C-NMR ($CDCl_3$): δ 170.51, 169.52, 169.46, 169.16 (C=O acetyl), 106.19 (C-1), 80.21, 77.95, 73.36, 68.73 (C-2, C-3, C-4, C-5)[7], 63.14 (C-6), 68.06 ($O\underline{CH_2}(CH_2)_2CH_3$), 31.35 ($OCH_2\underline{CH_2}CH_2CH_3$), 19.08 ($OCH_2CH_2\underline{CH_2}CH_3$), 13.68 ($OCH_2CH_2CH_2\underline{CH_3}$), 20.5 ($CH_3$ acetyl) ppm. Further elution gave

compound **7** (173 mg, 22%) also as a colourless oil. GLC-analysis: R_t 9.71 (98%). $[\alpha]_D$ $+140.3^0$ (EtOH). ^{1}H-NMR ($CDCl_3$): δ 5.53 (t, 1H, H-3), 5,26 (d, 1H, H-1), 5.18 (m, 1H, H-5), 4.91 (t, 1H, H-2), 4.5-4.3 (m, 2H, H4, H6a), 4.13 (dd, 1H, H-6b), 3.9-3.3 (m, 2H, $OC\underline{H}_2(CH_2)_2CH_3$), 2.1 (4s, 12H, CH_3 acetyl), 1.7-1.2 (m, 4H, $OCH_2(C\underline{H}_2)_2CH_3$), 0.91 (t, 3H, $OCH_2(CH_2)_2C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 170.50, 169.88, 169.67, 169.63 (C=O acetyl), 100.13 (C-1), 74.94, 78.30, 73.94, 67.96 (C-2, C-3, C-4, C-5)[7], 62.92 (C-6), 68.54 ($O\underline{C}H_2(CH_2)_2CH_3$), 31.38 ($OCH_2\underline{C}H_2CH_2CH_3$), 19.07 ($OCH_2CH_2\underline{C}H_2CH_3$), 13.65 ($OCH_2CH_2CH_2\underline{C}H_3$), 20.5 ($CH_3$ acetyl) ppm.

(c) *1-octanol (Table 2, entry 3).* A stirred solution of **2** (500 mg, 1.92 mmol) was treated with methanol (50 ml) containing iodine (25 mg, 0.05 equiv) as described above in (a). 1-Octanol (50 ml) was then added to the mixture which was concentrated *in vacuo* to remove exess methanol. The resulting solution was heated at 100^0C for 8 days, cooled, treated with a further quantity of iodine (250 mg, 0.52 equiv) and then heated for a further 24 h at 100^0C. The cooled product mixture was processed and acetylated as described above in (a). Column chromatography (hexane/ethyl acetate, 3:1) of the crude product afforded compound **8** (5 mg, 1%). GLC-analysis: R_t 16.35 (96%). $[\alpha]_D$ $+109.4^0$ (EtOH). ^{1}H-NMR ($CDCl_3$): δ 5.54 (t, 1H, H-3), 5,27 (d, 1H, H-1), 5.18 (m, 1H, H-5), 4.95 (t, 1H, H-2), 4.5-4.3 (m, 2H, H4, H6a), 4.15 (dd, 1H, H-6b), 3.9-3.3 (m, 2H, $OC\underline{H}_2(CH_2)_6CH_3$), 2.1 (4s, 12H, CH_3 acetyl), 1.7-1.2 (m, 12H, $OCH_2(C\underline{H}_2)_6CH_3$), 0.88 (t, 3H, $OCH_2(CH_2)_6C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 170.48, 169.86, 169.65, 169.60 (C=O acetyl), 100.20 (C-1), 74.91, 78.33, 73.91, 67.95 (C-2, C-3, C-4, C-5)[7], 62.88 (C-6), 68.51 ($O\underline{C}H_2(CH_2)_6CH_3$), 31.53 ($OCH_2(\underline{C}H_2)_6CH_3$), 13.85 ($OCH_2(CH_2)_6\underline{C}H_3$), 20.5 ($CH_3$ acetyl) ppm. Further elution gave **11** as a colourless oil (83 mg, 10%). GLC-analysis: R_t 17.28 (99%). $[\alpha]_D$ $+92.5^0$ (EtOH). ^{1}H-NMR ($CDCl_3$): δ 5.49 (d, 1H, H-3), 5.2-4.7 (m, 3H, H-1, H-2, H-4), 4.4-3.9 (m, 3H, H-5, H-6ab), 3.6-3.3 (m, 2H, $OC\underline{H}_2(CH_2)_6CH_3$), 2.1 (4s, 12H, CH_3 acetyl), 1.7-1.2 (m, 12H, $OCH_2(C\underline{H}_2)_6CH_3$), 0.88 (t, 3H, $OCH_2(CH_2)_6C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 170.56, 170.06, 169.55, 169.16 (C=O acetyl), 95.55 (C-1), 70.87, 70.19, 68.57, 67.05 (C-2, C-3, C-4, C-5)[7], 61.87 (C-6), 68.65 ($O\underline{C}H_2(CH_2)_6CH_3$), 31.72, 29.17 (3x), 25.94, 22.56 ($OCH_2(\underline{C}H_2)_6CH_3$), 14.00 ($OCH_2(CH_2)_6\underline{C}H_3$), 20.6 ($CH_3$ acetyl) ppm. This was followed by compound **14** (54 mg, 6%) also as an colourless oil. GLC-analysis: R_t 17.63 (99%). $[\alpha]_D$ -18.0^0 (EtOH), lit.[5] -20.5^0 ($CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 5.3-4.9 (m, 3H, H-2, H-3, H-4), 4.48 (d, 1H, H-1), 4.4-4.1 (m, 2H, H-6ab), 4.0-3.4 (m, 3H, H-5, $OC\underline{H}_2(CH_2)_6CH_3$), 2.1 (4s, 12H, CH_3 acetyl), 1.7-1.2 (m, 12H, $OCH_2(C\underline{H}_2)_6CH_3$), 0.87 (t, 3H, $OCH_2(CH_2)_6C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 170.64, 170.27, 169.35, 169.22 (C=O acetyl), 100.76 (C-1), 71.28, 72.81, 68.41, 71.66 (C-2, C-3, C-4, C-5)[7], 61.93 (C-6), 70.19 ($O\underline{C}H_2(CH_2)_6CH_3$), 31.72, 29.30, 29.18 (2x), 25.72, 22.56 ($OCH_2(\underline{C}H_2)_6CH_3$), 14.00 ($OCH_2(CH_2)_6\underline{C}H_3$), 20.6 ($CH_3$ acetyl) ppm.

(d) *1-octanol (Table 2, entry 4).* The diacetal **2** (500 mg, 1.92 mmol) was treated with methanol (50 ml) and iodine (25 mg, 0.05 equiv) as described above in (c). 1-Octanol (50 ml) was then added to the mixture which was concentrated *in vacuo* to remove exess methanol. The resulting solution was heated at 110^0C for 10 days. Column chromatography (hexane/ethyl acetate, 3:1) of the processed and acetylated (*vide supra)* crude product mixture afforded a mixture of the peracetates **5**, **8**, **11** and **14** as an colourless oil (729 mg, 82%). GLC-analysis: R_t 16.08 (**5**, 25%), 16.35 (**8**, 18%),

17.26 (**11**, 29%), 17,62 (**14**, 28%). ^{13}C-NMR ($CDCl_3$): characteristic C-1 signals for compounds **5**, **8**, **11** and **14** were observed at δ 106.05, 99.99, 95.39 and 100.55 ppm, respectively.

(e) *1-dodecanol (Table 2, entry 5).* Compound **2** was treated (1000 mg, 3.84 mmol) with methanol (50 ml) and iodine (50 mg, 0.05 equiv) as described in (a), cooled, treated with 1-dodecanol (50 ml), evaporated *in vacuo* to remove excess methanol and then heated at 90^{0}C for 6 days followed by 7 days at 130^{0}C. The cooled product mixture was processed and acetylated as described previously. Column chromatography (hexane/ethyl acetate, 3:1) of the crude product afforded compound **12** (384 mg, 20%). GLC-analysis[6]: R_t 10.05 (92%). $[\alpha]_D$ +76.7^0 (EtOH). ^{1}H-NMR ($CDCl_3$): δ 5.48 (d, 1H, H-3), 5.2-4.7 (m, 3H, H-1, H-2, H-4), 4.4-3.9 (m, 3H, H-5, H-6ab), 3.8-3.3 (m, 2H, $OC\underline{H}_2(CH_2)_{10}CH_3$), 2.1 (4s, 12H, CH_3 acetyl), 1.7-1.3 (m, 20H, $OCH_2(C\underline{H}_2)_{10}CH_3$), 0.87 (t, 3H, $OCH_2(CH_2)_6C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 170.27, 169.81 (2x), 169.33 (C=O acetyl), 95.43 (C-1), 70.75, 70.08, 68.96, 67.15 (C-2, C-3, C-4, C-5)[7], 61.75 (C-6), 68.48 ($O\underline{C}H_2(CH_2)_{10}CH_3$), 32.63, 31.71, 29.43, 28.19 (2x), 28.06, 25.84, 25.64, 25.34, 22.47 ($OCH_2(\underline{C}H_2)_{10}CH_3$), 13.98 ($OCH_2(CH_2)_{10}\underline{C}H_3$), 20.5 ($CH_3$ acetyl) ppm. Further elution gave **15** as a white solid. Recrystallization of the crude product (ethanol/water) gave pure **15** (83 mg, 10%), m.p. 58.0-58.5^{0}C, $[\alpha]_D$ -21.4^0 (EtOH); lit.[5] m.p. 58.5-59.5^{0}C, $[\alpha]_D$ -18.8^0. GLC-analysis[6]: R_t 10.45 (100%). ^{1}H-NMR ($CDCl_3$): δ 5.20 (t, 1H, $J_{3,4}$ 9.5 Hz, H-3), 5.09 (t, 1H, $J_{4,5}$ 9.6 Hz, H-4), 4.98 (t, 1H, $J_{2,3}$ 9.5 Hz, H-2), 4.49 (d, 1H, $J_{1,2}$ 8.0 Hz, H-1), 4.26 (dd, 1H, $J_{6a,6b}$ 12.3 Hz, $J_{6a,5}$ 4.7 Hz, H-6a), 4.13 (dd, 1H, $J_{6b,5}$ 2.3 Hz, H-6b), 3.87 (m, 2H, $OC\underline{H}_2(CH_2)_{10}CH_3$), 3.68 (m, 1H, H-5), 3.47 (m, 1H, $OC\underline{H}_2(CH_2)_{10}CH_3$), 2.1 (4s, 12H, CH_3 acetyl), 1.58 (m, 2H, $OCH_2C\underline{H}_2(CH_2)_9CH_3$), 1.25 (m, 18H, $OCH_2CH_2(C\underline{H}_2)_9CH_3$), 0.88 (t, 3H, $OCH_2CH_2(CH_2)_9C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 170.69, 170.31, 169.39, 169.26 (C=O acetyl), 100.83 (C-1), 71.37, 72.88, 68.50, 71.74 (C-3, C-5, C-2, C-4)[7], 62.00 (C-6), 70.25 ($O\underline{C}H_2(CH_2)_{10}CH_3$), 31.90, 29.61 (2x), 29.34 (2x), 27.14, 25.80, 22.67 ($OCH_2(\underline{C}H_2)_{10}CH_3$), 14.10 ($OCH_2(CH_2)_{10}\underline{C}H_3$), 20.6 ($CH_3$ acetyl) ppm.

(f) *1-dodecanol (Table 2, entry 6).* The diacetal **2** (1000 mg, 3.84 mmol) was treated with methanol (50 ml) and iodine (50 mg, 0.05 equiv), followed by 1-dodecanol (50 ml) as described above in (c) and then heated at 100^{0}C for 6 days. Column chromatography (hexane/ethyl acetate, 3:1) of the processed and acetylated *(vide supra)* crude product afforded a mixture of the peracetates **6**, **9**, **12** and **15** as a colourless oil (1196 mg, 61%). GLC-analysis: R_t 9.85 (**6**, 25%), 9.93 (**9**, 18%), 10.22 (**12**, 29%), 10.50 (**15**, 28%). ^{13}C-NMR ($CDCl_3$): characteristic C-1 signals for **6**, **9**, **12** and **15** were observed at δ 106.05, 99.99, 95.39 and 100.55 ppm, respectively.

6.4 References and notes

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6. A different temperature programme was used: 200-260^{0}C at 10^{0}C/min followed by 260^{0}C for 10 min.
7. Signals may be interchanged.

SYNTHESIS OF SOME POTENTIAL SURFACTANTS DERIVED FROM D-GLUCOSE AND D-FRUCTOSE

7.1 Introduction

Carbohydrates are neutral and hydrophilic and can be used as potential head-groups for surfactants or amphiphiles. Surfactants are molecules with an amphiphilic structure which contains both a hydrophobic and a hydrophilic structural unit with different solubility properties. For sugar surfactants the hydrophilic part comprises a carbohydrate fragment and the hydrophobic part contains one or two long aliphatic chains which gives these compounds the property of surface activity. The term surfactant is a contraction of "surface active agent". At phase borders, surfactants are oriented usually in mono-layers and only above a characteristic limiting concentration, *e.g.* the critical micelle concentration (CMC), formation of aggregrates occurs and micelles, vesicles or bi-layers are formed. The CMC and the surface tension at the CMC (γ_{CMC}) are characteristic values for each surfactant. The CMC-value depends on the hydrophobicity of the aliphatic chain, the charge of the head-group, the type of counter-ion of the head-group and the presence of other electrolytes[1]. In addition some pure carbohydrate amphiphiles also have liquid crystal properties[2].

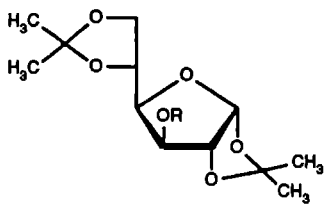
Carbohydrates such as D-glucose and D-fructose are attractive and inexpensive starting materials for the synthesis of various surfactants. The use of surfactants based on the naturally occurring carbohydrates is particularly advantageous since most of these compounds are non-allergenic, non-toxic and readily biodegradable which makes them suitable for use in consumer products. Some sucrose monoesters of long-chain fatty acids are currently commercially available[3] for formulation as detergents for domestic use, and for use as emulsifying agents in food and cosmetics, due to their good non-toxic and dermatological properties[4,5]. In some countries, *e.g.* Japan, France and Switzerland, sucrose esters are now permitted as food additives. The long-chain alkyl D-glycosides (Chapter 5) and the alkyl (poly)glucosides (APG's) are another interesting class of sugar surfactants, which currently find application as detergents and emulsifiers in cosmetic products such as shampoos (*e.g.* lauryl polyglucose, produced by Henkel), or in food[6]. For the use of sugar-surfactants in domestic or industrial detergents, efficacy is important, and they have to be produced at low competitive costs compared to the conventional petroleum-derived anionic and nonionic surfactants.

In this Chapter, the emphasis of the research was on the synthesis of some non-ionic and anionic surfactants based on D-glucose and D-fructose, rather than on the determination of special physical properties of these possible surfactant compounds. The di-*O*-isopropylidene acetals of D-glucose (**1**) and D-fructose (**2**, **3**) are potentially attractive intermediates for the synthesis of

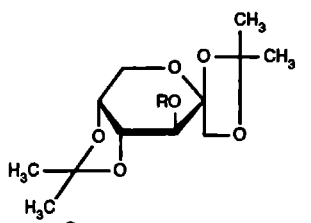
sugar-based amphiphiles since they are protected and possess only one free hydroxyl group which can be functionalized with an appropriate aliphatic chain. These acetals are readily available and can be obtained by the use of the iodine-catalyzed acetalation method[7] described in Chapter 3. In section 7.2 the synthesis of non-ionic long-chain alkanesulphonyl esters is described. Section 7.3 deals with the synthesis of some long-chain alkylsulphonic ethers.

7.2 Synthesis of alkanesulphonyl esters

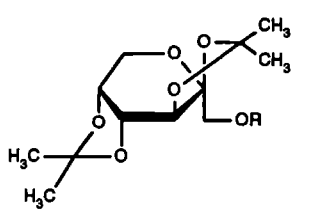
Sulphonate esters, *e.g.* tosylates and mesylates, of the readily accessible di-*O*-isopropylidene acetals of D-glucose and D-fructose are known to be stable compounds, more stable for example than the corresponding acetates or benzoates. It was decided therefore to investigate the synthesis of these type of esters but with longer alkyl-chains as potential surfactants. 1-Decanesulphonyl chloride (**4**) and dodecylbenzenesulphonyl chloride (**5**) were used as sulphonylating reagents in pyridine in the standard procedure with the acetals **1**, **2** and **3**. The sulphonyl chloride **4** is readily available from 1-decanesulphonic acid and the sulphonyl chloride **5** from dodecylbenzenesulphonic acid by treatment with thionyl chloride in the presence of a catalytic amount of DMF[8]. The latter sulphonic acid, which is a mixture of isomers (97% *para*, 3% *ortho/meta*), is an inexpensive reagent and used frequently in the synthesis of surfactants. The reaction conditions and the results obtained are listed in Table 1.



1 R = H
6 R = $SO_2(CH_2)_9CH_3$
9 R = $SO_2C_6H_4(CH_2)_{11}CH_3$



2 R = H
7 R = $SO_2(CH_2)_9CH_3$
10 R = $SO_2C_6H_4(CH_2)_{11}CH_3$



3 R = H
8 R = $SO_2(CH_2)_9CH_3$
11 R = $SO_2C_6H_4(CH_2)_{11}CH_3$

Table 1

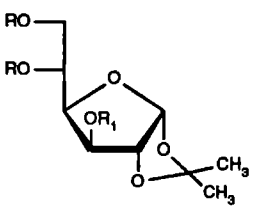
Substrate	Reagent [a]	Time	Product [b]	Yield
1	**4**	2 d	**6**	78 %
2	**4**	4 d	**7**	91 %
3	**4**	3 d	**8**	80 %
1	**5**	6 d	**9**	79 %
2	**5**	2 d	**10**	59 %
3	**5**	2 d	**11**	96%

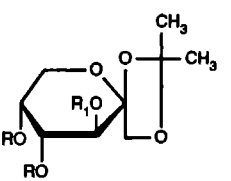
a) **4** = 1-decanesulphonyl chloride, **5** = dodecylbenzenesulphonyl chloride.
b) All products showed a correct elemental analysis and (Cl^+) mass spectrum.

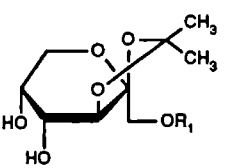
Compounds **1**, **2** and **3** were treated with 1.0-1.5 equivalents of the respective sulphonylating reagents **4** or **5** under standard conditions in pyridine (Table 1). The reactions were conveniently monitored by TLC-analysis and performed for 2 to 6 days at room temperature. The excesses of the akylsulphonyl reagents **4** and **5** were removed from the crude products by column chromatography and the corresponding alkanesulphonyl esters **6-11** could be isolated as pure compounds in good yields (59-96%). The alkanesulphonyl esters obtained were not crystalline and were isolated as oils. The products were fully characterized by elemental analysis, mass spectroscopy (CI^+) and by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

From these results it may be concluded that the diacetals **1**, **2** and **3** can be used for the synthesis of interesting and well defined 1-decane and dodecylbenzene sulphonic esters using a simple esterification procedure. The obtained products **6-11** exhibited some foaming properties when they were brought into contact with water and these compounds may possibly be useful as surfactants. To increase the hydrophilicity of the carbohydrate head-group, it is necessary to remove the isopropylidene protecting groups by hydrolysis. The hydrolysis of compounds **6**, **7** and **8** was subsequently investigated.

Acetal functions are generally removed by acid-catalyzed hydrolysis. It is known that there are differences in the stability of various types. In general, cyclic acetals attached to the anomeric carbon are more stable towards acid hydrolysis than those which are attached to other positions, and *cis*-fused acetals on a furanose ring are more stable than *exo*-cyclic acetals[9]. The *spiro*-acetal group of D-fructose, *e.g.* the 1,2-*O*-isopropylidene group in compound **2**, is one of the more stable type of acetal groups. Selective removal of isopropylidene acetal functions can be readily achieved with the use of 80% aqueous acetic acid. An alternative method for the deprotection of some acetals is by treatment with dilute solutions of iodine in methanol[10] (see Chapter 5 and 6). In these studies[10] selective hydrolysis of the acetals was claimed using short reaction times at room temperature and this method was, therefore, also investigated. The reaction conditions and the results obtained are depicted in Table 2.







12 $R_1 = SO_2(CH_2)_9CH_3$, R = H
13 $R_1 = SO_2(CH_2)_9CH_3$, R = Ac

14 $R_1 = SO_2(CH_2)_9CH_3$, R = H
15 $R_1 = SO_2(CH_2)_9CH_3$, R = Ac

16 $R_1 = SO_2(CH_2)_9CH_3$

Table 2 Selective hydrolysis of the alkanesulphonyl esters 6, 7 and 8.

80% aqueous AcOH				I_2 / MeOH / RT				
Substrate	Time	Product	Yield	Substrate	I_2 (w/v)	Time	Product	Yield
6	3 d	**12**	79%	**6**	0.5%	2 d	**12**	79%
7	7 d	**14**	44% [b]	**7**	1.0%	1.5 d	**14**	51% [b]
8	> 7 d	a	-	**8**	1.0%	10 d	a	-

a) Selective hydrolysis was not possible. b) after recrystallization.

When 1-decanesulphonyl ester **6** was treated with 80% aqueous acetic acid, at room temperature for 3 days, compound **12** could be isolated in 79% yield. As expected, compound **6** was selectively hydrolysed at the *exo*-cyclic 5,6-position in this reaction. Compound **12** was acetylated in the usual manner and characterized as the corresponding acetate **13**. The same result was obtained in the reaction of **6** with iodine (0.5% w/v) in methanol at room temperature for 2 days, and compound **12** was isolated in the same yield (79%).

Treatment of **7** with 80% aqueous acetic acid at room temperature for 7 days afforded the expected compound **14**, which was obtained as a crystalline solid (44%). The *cis*-fused 4,5-*O*-isopropylidene acetal of **7** was selectively removed during this reaction. The resulting compound **14** was further characterized as the corresponding acetate **15**. A similar result was obtained by treatment of **7** with iodine (1% w/v) in methanol at room temperature, but a shorter reaction time was required (1.5 day) and compound **14** could be isolated in a slightly higher yield (51%).

Selective hydrolysis of the 1-decanesulphonyl ester **8** to yield compound **16** was unsuccessful using either method. Only mixtures of partially and fully deprotected derivatives could be detected (TLC) in the reaction mixtures and no further attempts were undertaken to achieve selective hydrolysis of compound **8**.

The complete hydrolysis of the 1-decanesulphonyl esters **6**, **7** and **8** was subsequently investigated. To achieve the removal of all of the isopropylidene functions the method using dilute solutions of iodine in methanol[11] was again used, but with heating under reflux for longer periods. Derivatives with a free hydroxyl group at the anomeric center are converted into mixtures composed of methyl glycosides by this treatment (see Chapter 5 and 6). Reaction of compound **6**, **7** and **8** under these conditions afforded mixtures of the corresponding methyl glycosides (Scheme 1). The reaction conditions and the results obtained are listed in Table 3.

Scheme 1

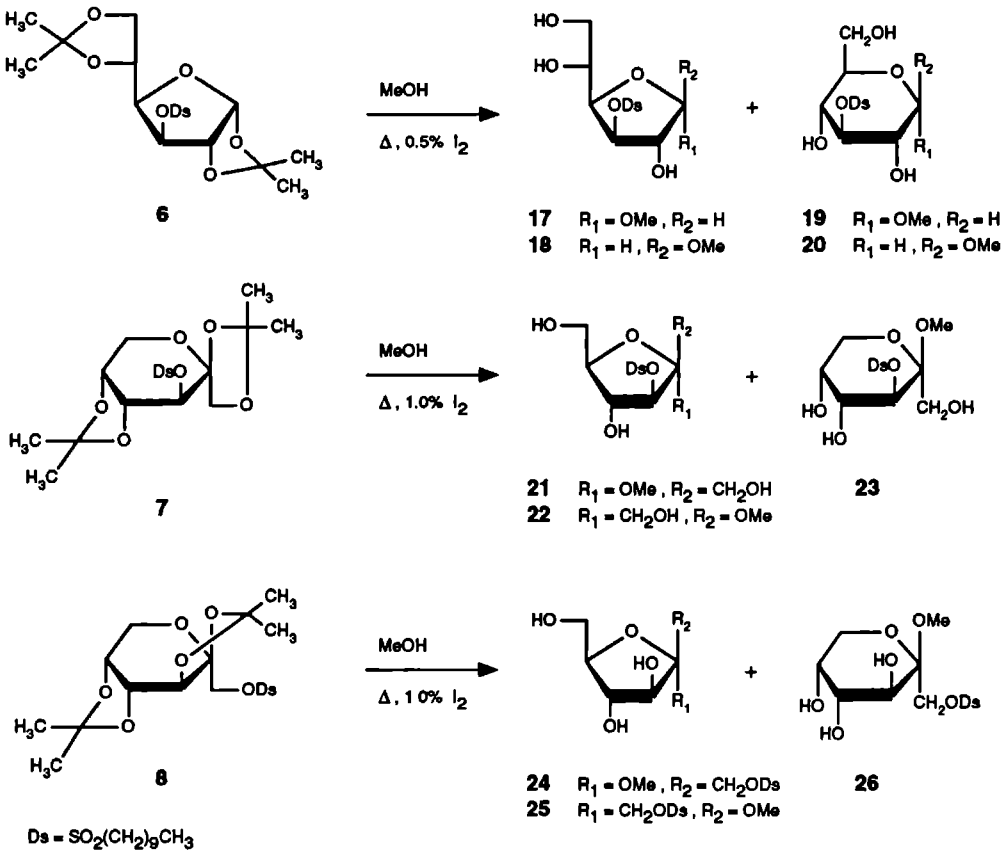


Table 3 Complete hydrolysis of acetals 6, 7, and 8.

Substrate	I_2 (w/v)	Time	Product(s)	Composition [a]	Yield [b]
6	0.5%	10 h	**17** + **18** + **19** + **20**	7 : 5 : 25 : 63	36%
7	1.0%	8 h	**21** + **22** + **23**	53 : 34 : 14	59% [c]
8	1.0%	14 h	**24** + **25** + **26**	49 : 35 : 16	76% [d]

a) determined by ^{13}C-NMR (IGDE). b) total yield after column chromatography.
c) pure **21** isolated in 31% yield.
d) pure **24** isolated in 37% yield.

When the ester **6** was treated with iodine (0.5% w/v) in boiling methanol for 10 h, analysis (TLC) indicated the presence of four products, with mobilities expected for the methyl D-glucosides. NMR-analysis of the isolated product mixture also revealed the presence of four individual

components which were identified as the methyl α-D-glucofuranoside (**17**), methyl β-D-glucofuranoside (**18**), methyl α-D-glucopyranoside (**19**) and methyl β-D-glucopyranoside (**20**). The identities of these products were substantiated by ^{13}C-NMR spectroscopy using an inverse gate decoupling technique[11] (see also Chapter 5). The ^{13}C-NMR spectrum showed the presence of the signals expected for the anomeric carbon atoms assigned to compounds **17** (δ(C-1): 103.9 ppm), **18** (δ(C-1): 112.7 ppm), **19** (δ(C-1): 101.9 ppm), and **20** (δ(C-1): 109.4 ppm). Integration of the ^{13}C signals gave an indication of the product ratio, for **17**:**18**:**19**:**20**, which was shown to be 7:5:25:63. It was difficult to separate the product mixture further by column chromatography and no further attempts were undertaken in that direction.

Treatment of **7** with iodine (1.0% w/v) in boiling methanol for 8 h, resulted in a product mixture which was shown to contain the methyl D-fructosides **21**, **22** and **23** which, in contrast to the methyl D-glucosides, could be purified further by column chromatography. In this manner the pure methyl α-D-fructofuranoside **21** (31%) was obtained, together with a mixture of methyl β-D-fructofuranoside **22** and methyl β-D-fructopyranoside **23** (28%) which were shown to be present in a ratio of 7:3.

When compound **8** was treated with iodine (1% w/v) in boiling methanol for 14 h, analysis of the resulting product mixture revealed the presence of the methyl D-fructosides **24**, **25** and **26**. Column chromatography of the product mixture afforded pure methyl α-D-fructofuranoside **24** (37%), together with a mixture of methyl β-D-fructofuranoside **25** and methyl β-D-fructopyranoside **26** (39%), in a ratio of 7:3

It may be concluded that the deprotection of the isopropylidene functions of the non-ionic alkylsulphonyl esters, to increase the hydrophilicity of the carbohydrate head-group, can be achieved using simple methods. Selective hydrolysis of one of the two isopropylidene functions is possible by the use of 80% aqueous acetic acid or with dilute solutions of iodine in methanol at room temperature. To achieve complete hydrolysis dilute solutions of iodine in boiling methanol can be used, which leads to mixtures of the corresponding methyl glycosides. For practical purposes, however, *i.e.* in possible application as detergents, these mixtures could be used as such. All of the products obtained were isolated as stable compounds and exhibited good foaming properties. In order to evaluate the non-ionic esters obtained as suitable surfactants or the determination of some additional physical properties, such as the critical micelle concentration (CMC) and surface tension, further studies would be required.

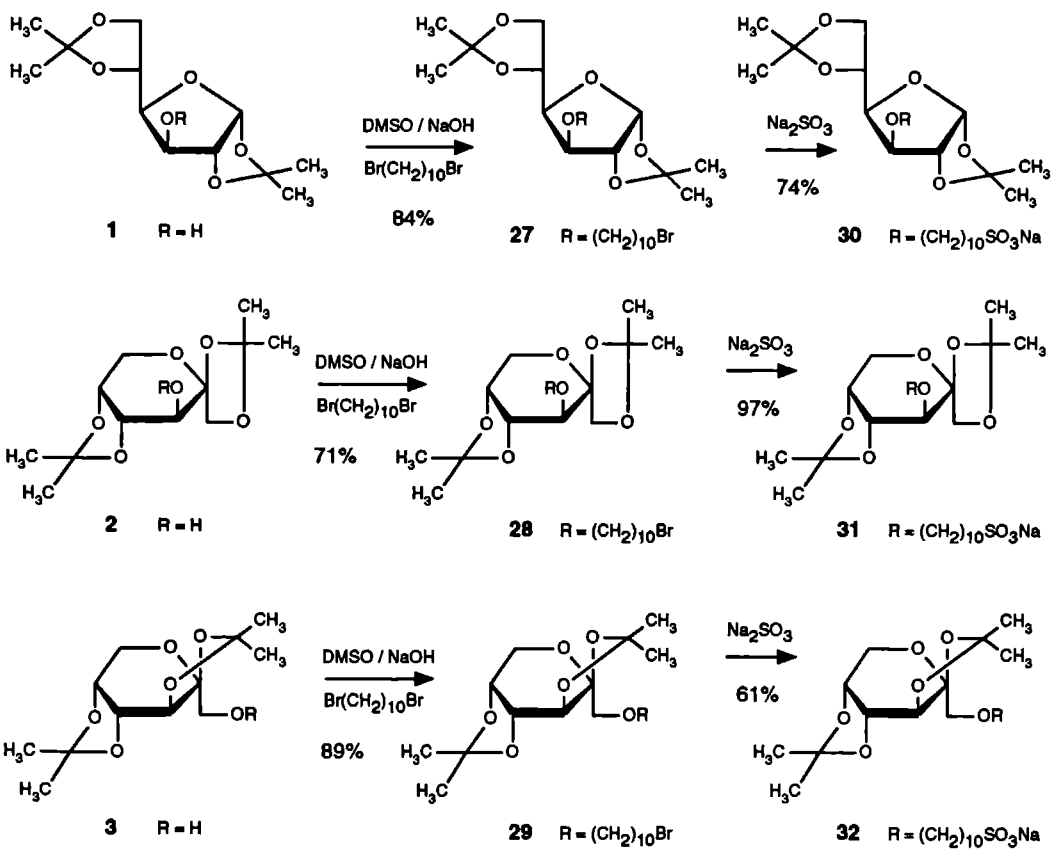
7.3 Synthesis of ether sulphonates of D-glucose and D-fructose

The di-*O*-isopropylidene acetals **1**, **2** or **3** can also be functionalized with an aliphatic chain via an ether linkage, as an alternative to ester formation (section 7.2). In general ether linkages possess greater chemical stabilities. When alkyl ethers are also functionalized at the end of the aliphatic chain they can be substituted at a later stage for instance with an extra polar head-group. In this section the synthesis of the ionic 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose

3-decylsulphonate **30**, 1,2:4,5-*O*-isopropylidene-β-D-fructopyranose 3-decylsulphonate **31** and 2,3:4,5-*O*-isopropylidene-β-D-fructopyranose 1-decylsulphonate **32** from the diacetals **1**, **2** and **3** is described. These compounds could also be of interest as ionic-surfactants with potential application as detergents or emulsifiers.

The alkylation of compounds **1**, **2** and **3** was achieved using an efficient etherification procedure described in the literature[12]. In this method a free hydoxyl group is alkylated by treatment of the substrate in DMSO with an alkyl halide (3 equiv) in the presence of finely powdered sodium hydroxide (3 equiv). This type of alkylation has also been carried out previously in either DMSO or DMF using sodium hydride as the base[13]. The use of solid potassium or sodium hydroxide however prevents the formation of the $CH_3SOCH_2^-$ anion that could lead to some unwanted by-products. It was found[12] that an excess of sodium hydroxide as base (≥ 3 equiv) and 3-5 equivalents of akyl halide per available hydroxyl function gave the best results. This procedure was adopted for the preparation of the bromodecyl ethers **27-29** from the acetals **1-3** by reaction with the bifunctional 1,10-dibromodecane. In the second step the alkyl ethers **27-29** were transformed into the corresponding sulphonate ethers **30-32** by treatment with sodium sulphite (Scheme 2).

Scheme 2



In the alkylation reactions the order of addition of the reagents was important. To prevent dimerisation, the solution of the diacetal was directly added to a solution of 1,10-dibromodecane in DMSO containing sodium hydroxide, rather than by the addition of the alkyl halide to a solution of the diacetal containing sodium hydroxide as described in the original procedure[12]. Treatment of a solution of 1,10-dibromodecane (3 equiv) in DMSO containing powdered sodium hydroxide (3 equiv) with the diacetal **1** for 10 h at room temperature afforded the corresponding 3-*O*-bromodecyl ether (**27**, 84%) which was isolated by column chromatography. The corresponding 3-*O*-bromodecyl-1,2:4,5-*O*-isopropylidene-β-D-fructopyranose (**28**) and 1-*O*-bromodecyl-2,3:4,5-*O*-isopropylidene-β-D-fructopyranose (**29**) were obtained from the diacetals **2** and **3** under similar conditions and were isolated in yields of 71% and 89%, respectively. During the alkylation reactions small amounts of the corresponding decenes (GLC, 5-10%) were formed as by-products. These were difficult to separate from the ethers **27-29** by column chromatography. The decenes, however, did not have an adverse effect on the subsequent sulphonation steps.

The sulphonation reactions of the bromodecyl ethers were performed using sodium sulphite[15]. Treatment of the bromodecyl ethers **27-29** with sodium sulphite in a boiling mixture of ethanol and water for 17 h gave the corresponding decylsulphonates **30-32** in 69-97% yield. During the work-up procedures the contaminating decenes were removed easily from the crude products by washing with diisopropyl ether. The decylsulphonate ethers **30-32** obtained were very soluble in water and produced large volume, stable foams upon agitation.

The procedures described here represent a convenient synthetic route to the decylsulphonate ethers **30**, **31** and **32** starting from the di-*O*-isopropylidene acetals of D-glucose and D-fructose in overall yields of 57%, 69% and 60% respectively, and requiring only two reaction steps. It would be of interest to investigate further the physical properties of these compounds, *i.e.* the critical micelle concentration (CMC) and surface tension, to establish their potential application in practical products as detergents or emulsifiers.

7.4 Experimental

General methods

Optical rotations were determined with a Perkin-Elmer automatic polarimeter, model 241 MC on 1% solutions at 20°C. Thin-layer chromatography (TLC) on pre-coated plates of silica gel (Merck) was performed with dichloromethane - methanol (4/1, v/v, solvent A) or hexane - ethyl acetate (1/1, v/v, solvent B). Detection was affected by spraying with 3% H_2SO_4 in ethanol followed by heating at 140°C. GLC was performed with a Hewlett-Packard 5790 or 5890 series II gaschromatograph using a fused silica capillary column (25m) coated with HP-1 cross-linked methyl silicone gumphase operating at 100-150°C; 100°C (isothermally, 5 min) followed by 5°C/min for 10 min; or a temperature programme from 100-250°C at 15°C/min, followed by 10 min at 250°C (isothermal), with nitrogen as the carrier gas (2 ml/min). Compounds were identified by co-injection with authentic samples and the percentages composition of the analysed mixtures are all relative.

Melting points were determined on a Reichert thermopan microscope and are uncorrected. Elemental analysis were performed on a Carlo Erba Instruments CHNS-O EA 1108 element analyzer. Mass spectra were recorded using a double focussing VG 7070E mass spectrometer using the chemical ionisation (CI) technique, with methane as reaction gas. ^{1}H-NMR spectra were recorded with a Bruker AC 100 (100 MHz) or Bruker AM 400 (400 MHz) spectrometer on solutions in $CDCl_3$ (internal standard Me_4Si) or D_2O. ^{13}C-NMR spectra were recorded with a Bruker AC 100 or Bruker AM 400 spectrometer operating at 25 and 100.6 MHz, respectively, on solutions in $CDCl_3$ (internal Me_4Si) or D_2O (external dioxane at 76.8 ppm). Pyridine was distilled from potassium hydroxide and hexane from calcium hydride before use.

1-Decanesulphonyl chloride (**4**). A stirred mixture of 1-decanesulphonic acid, sodium salt (5.00 g, 20.5 mmol) in thionyl chloride (6 ml) was heated under reflux for 15 min, whereon DMF (0.1 ml) was added[8] and the mixture heated under reflux for a further 1 h. The cooled mixture was concentrated *in vacuo*, the crude residue dissolved in CH_2Cl_2, washed with 10% aqueous NaCl, dried (Na_2SO_4) and concentrated *in vacuo* to afford **4** as a waxy solid (4.90 g, 99%). IR(KBr) υ_{max} 2900 (CH_2), 1375 (SO_2 as), 1160 (SO_2 ss) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.66 (t, 2H, $RC\underline{H}_2SO_2Cl$), 2.05 (m, 2H, $RC\underline{H}_2CH_2SO_2Cl$), 1.28 (m, 14H, $CH_3(C\underline{H}_2)_7CH_2CH_2SO_2Cl$), 0.88 (t, 3H, CH_3) ppm.

Dodecylbenzenesulphonyl chloride (**5**). A stirred mixture of dodecylbenzenesulphonic acid (11 ml, 40 mmol) in thionyl chloride (12 ml) was heated under reflux for 15 min, whereon DMF (0.1 ml) was added[8] and the mixture was heated under reflux for a further 45 min. The cooled mixture was concentrated *in vacuo* and toluene (3 x 10 ml) was distilled *in vacuo* from the residue to afford **5** as a dark syrup (13.46 g, 98%). IR(KBr) υ_{max} 2900 (CH_2), 1375 (SO_2 as), 1175 (SO_2 ss), 1590 (aromatic) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 7.90, 7.04 (m, 4H, phenyl), 1.66 (m, 2H, $RC\underline{H}_2C_6H_4SO_2Cl$), 1.23 (m, 20H, $CH_3(C\underline{H}_2)_{10}CH_2C_6H_4SO_2Cl$), 0.85 (t, 3H, CH_3) ppm.

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose 3-(1'-decanesulphonate) (**6**). To a cooled (0^{0}C), stirred solution of **1** (2.00 g, 7.7 mmol) in pyridine (4 ml) **4** (2.05 g, 8.5 mmol) was added and the mixture was then stirred at room temperature for 2 d. The mixture was treated with ice water (2 ml) and after 5 min dissolved in ethyl acetate (30 ml). The solution was washed with 10% aqueous sodium chloride solution (3 x 15 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (hexane/ethyl acetate, 3:1) of the crude product afforded **6** as a yellow oil (2.79 g, 78%). $[\alpha]_D$ -42.8^0 ($CHCl_3$), GLC-analysis: R_t 14.78 (100%). Calculated for $C_{22}H_{40}SO_8$ (464.60): C 56.87%, H 8.68%; Found: C 56.0%, H 8.2%. CI-MS: *m/z* 465 (M^+ + 1), 449 (M^+ - CH_3), 243 (M^+ - $CH_3(CH_2)_9SO_2O$), 185 (M^+ - $CH_3(CH_2)_9SO_2O$ - $(CH_3)_2CO$). ^{1}H-NMR ($CDCl_3$): δ 5.94 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.97 (d, 1H, $J_{3,4}$ 2.9 Hz, H-3), 4.82 (d, 1H, H-2), 4.22 (m, 1H, H-6a), 4.16 (dd, 1H, $J_{4,5}$ 8.8 Hz, H-4), 4.14 (dd, 1H, $J_{6b,6a}$ 11.7 Hz, H-6b), 4.02 (dd, 1H, $J_{5,6a}$ 4.4 Hz, H-5), 3.18 (m, 2H, $OSO_2C\underline{H}_2CH_2CH_2(CH_2)_6CH_3$), 1.89 (m, 2H, $OSO_2CH_2C\underline{H}_2CH_2(CH_2)_6CH_3$), 1.41 (m, 2H, $OSO_2CH_2CH_2C\underline{H}_2(CH_2)_6CH_3$), 1.26 (m, 12H, $OSO_2CH_2CH_2CH_2(C\underline{H}_2)_6CH_3$), 1.51, 1.43, 1.33, 1.32 (4s, 12H, CH_3), 0.88 (t, 3H, $ORC\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 112.61, 109.57 (qC, acetal), 105.11

(C-1), 83.78, 82.23, 79.87, 72.04 (C-2, C-5, C-3, C-4)[14], 67.56 (C-6), 51.21, 31.80, 29.42, 29.24, 28.94, 28.24, 23.27, 22.61 ($OSO_2(\underline{C}H_2)_9CH_3$), 26.92, 26.63, 26.16, 25.17 ($\underline{C}H_3$ acetal), 14.05 ($OSO_2(CH_2)_9\underline{C}H_3$) ppm.

1,2:4,5-Di-O-isopropylidene-β-D-fructopyranose 3-(1'-decanesulphonate) (**7**). Treatment of **2** (1.50 g, 5.8 mmol) in pyridine (4 ml) with **4** (2.22 g, 9.2 mmol) in the same manner as described above, but for 4 d, followed by column chromatography (hexane/ethyl acetate, 3:1) of the crude product afforded **7** as a yellow oil (2.43 g, 91%). $[\alpha]_D$ -120.1^0 ($CHCl_3$), GLC-analysis: R_t 14.42 (100%). Calculated for $C_{22}H_{40}SO_8$ (464.60): C 56.87%, H 8.68%; Found: C 56.0%, H 8.5%. CI-MS: *m/z* 465 (M^+ + 1), 449 (M^+ - CH_3), 243 (M^+ - $CH_3(CH_2)_9SO_2O$), 185 (M^+ - $CH_3(CH_2)_9SO_2O$ - $(CH_3)_2CO$), 143 (M^+ - $CH_3(CH_2)_9SO_2O$ - $(CH_3)_2CO$ - $C(CH_3)_2$). ^{1}H-NMR ($CDCl_3$): δ 4.58 (d, 1H, $J_{3,4}$ 7.8 Hz, H-3), 4.34 (dd, 1H, $J_{4,5}$ 5.3 Hz, H-4), 4.25 (m, 1H, H-5), 4.23, 4.21 (2s, 2H, H-1ab), 4.10 (dd, 1H, $J_{6a,6b}$ 11.7 Hz, H-6a), 4.02 (d, 1H, H-6b), 3.30 (m, 2H, $OSO_2C\underline{H}_2CH_2CH_2(CH_2)_6CH_3$), 1.90 (m, 2H, $OSO_2CH_2C\underline{H}_2CH_2(CH_2)_6CH_3$), 1.43 (m, 2H, $OSO_2CH_2CH_2C\underline{H}_2(CH_2)_6CH_3$), 1.27 (m, 12H, $OSO_2CH_2CH_2CH_2(C\underline{H}_2)_6CH_3$), 1.58, 1.50, 1.42, 1.38 (4s, 12H, CH_3), 0.88 (t, 3H, $ORC\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 112.66, 109.78 (qC, acetal), 103.18 (C-2), 78.33, 75.00, 74.12 (C-3, C-4, C-5)[14], 71.44 (C-1), 59.93 (C-6), 51.73, 31.79, 29.41, 29.26, 28.87, 28.08, 23.33, 22.60 ($OSO_2(\underline{C}H_2)_9CH_3$), 27.91, 26.64, 26.44, 26.23 ($\underline{C}H_3$ acetal), 14.04 ($OSO_2(CH_2)_9\underline{C}H_3$) ppm.

2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose 1-(1'-decanesulphonate) (**8**). A stirred cooled solution of the diacetal **3** (1.50 g, 5.8 mmol) in pyridine (4 ml) was treated with **4** (1.54 g, 6.4 mmol) in the same manner as described above, but for 3 d, followed by column chromatography (hexane/ethyl acetate, 6:1) of the crude product to afford **8** as a colourless oil (2.14 g, 80%). $[\alpha]_D$ -54.2^0 ($CHCl_3$), GLC-analysis: R_t 15.89 (100%). Calculated for $C_{22}H_{40}SO_8$ (464.60): C 56.87%, H 8.68%; Found: C 57.0%, H 8.5%. CI-MS: *m/z* 465 (M^+ + 1), 449 (M^+ - CH_3), 243 (M^+ - $CH_3(CH_2)_9SO_2O$), 185 (M^+ - $CH_3(CH_2)_9SO_2O$ - $(CH_3)_2CO$), 143 (M^+ - $CH_3(CH_2)_9SO_2O$ - $(CH_3)_2CO$ - $C(CH_3)_2$). ^{1}H-NMR ($CDCl_3$): δ 4.62 (dd, 1H, $J_{4,5}$ 7.9 Hz, H-4), 4.33 (d, 1H, $J_{3,4}$ 2.6 Hz, H-3), 4.27 (d, 1H, $J_{1a,1b}$ 10.7 Hz, H1a), 4.25 (dd, 1H, H-5), 4.20 (d, 1H, H1b), 3.92 (dd, 1H, $J_{6a,6b}$ 13.0 Hz, $J_{6a,5}$ 1.7 Hz, H-6a), 3.77 (d, 1H, H-6b), 3.14 (m, 2H, $OSO_2C\underline{H}_2CH_2CH_2(CH_2)_6CH_3$), 1.88 (m, 2H, $OSO_2CH_2C\underline{H}_2CH_2(CH_2)_6CH_3$), 1.42 (m, 2H, $OSO_2CH_2CH_2C\underline{H}_2(CH_2)_6CH_3$), 1.26 (m, 12H, $OSO_2CH_2CH_2CH_2(C\underline{H}_2)_6CH_3$), 1.55, 1.48, 1.42, 1.35 (4s, 12H, CH_3), 0.88 (t, 3H, $ORC\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 109.22, 109.15 (qC, acetal), 100.70 (C-2), 70.58, 70.15, 69.85 (C-3, C-4, C-5)[14], 69.26 (C-1), 61.37 (C-6), 50.48, 31.79, 29.40, 29.19, 28.92, 28.14, 23.24, 22.61 ($OSO_2(\underline{C}H_2)_9CH_3$), 26.46, 25.82, 25.21, 23.95 ($\underline{C}H_3$ acetal), 14.05 ($OSO_2(CH_2)_9\underline{C}H_3$) ppm.

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose 3-(p-dodecylbenzenesulphonate) (**9**). To a stirred, cooled (0^{0}C) solution of **1** (1.50 g, 5.8 mmol) in pyridine (4 ml) **5** (2.22 g, 6.4 mmol) was added and the mixture was then stirred at room temperature for 6 d. The mixture was treated with ice water (2 ml) and after 5 min dissolved in ethyl acetate (30 ml). The solution was washed with 10% aqueous sodium chloride solution (3 x 15 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (hexane/ethyl acetate, 5:1) of the crude product afforded **9** as an orange oil (1.86 g, 57%). $[\alpha]_D$ -43.3^0 ($CHCl_3$). Calculated for $C_{30}H_{48}SO_8$ (568.75): C 63.35%, H 8.51%; Found: C

63.0%, H 8.5%. CI-MS: *m/z* 569 ($M^+ + 1$), 555 ($M^+ + 1 - CH_2$), 243 ($M^+ - CH_3(CH_2)_{11}C_6H_4SO_2O$), 185 ($M^+ - CH_3(CH_2)_{11}C_6H_4SO_2O - (CH_3)_2CO$). ^{1}H-NMR ($CDCl_3$): δ 7.87, 7.32 (m, 4H, phenyl), 5.93 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.83 (d, 1H, H-3), 4.81 (d, 1H, H-2), 4.10 (m, 2H, H-6ab), 4.02 (m, 1H, H-4), 3.92 (m, 1H, H-5), 1.65 (m, 2H, $OSO_2C_6H_4C\underline{H}_2CH_2(CH_2)_9CH_3$), 1.55 (m, 2H, $OSO_2C_6H_4CH_2C\underline{H}_2(CH_2)_9CH_3$), 1.17 (m, 18H, $OSO_2C_6H_4CH_2CH_2(C\underline{H}_2)_9CH_3$), 1.48, 1.31, 1.26, 1.17 (4s, 12H, CH_3), 0.84 (t, 3H, $ORC\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 155-127 (6x, phenyl), 112.43, 109.08 (qC, acetal), 105.05 (C-1), 83.21, 82.02, 79.84, 71.81 (C-2, C-5, C-3, C-4)[14], 67.10 (C-6), 48-20 ($OSO_2C_6H_4(\underline{C}H_2)_{11}CH_3$), 26.59, 26.13, 25.06, 23.19 ($\underline{C}H_3$ acetal), 14.03 ($OSO_2Ph(CH_2)_{11}\underline{C}H_3$) ppm.

1,2:4,5-Di-O-isopropylidene-β-D-fructopyranose 3-(p-dodecylbenzenesulphonate) (**10**). Treatment of **2** (1.50 g, 5.8 mmol) in pyridine (4 ml) with **5** (2.56 g, 7.4 mmol) in the same manner as described above, but for 2 d, followed by column chromatography (hexane/ethyl acetate, 3:1) of the crude product afforded **10** as an orange oil (1.57 g, 48%). $[\alpha]_D$ -131.8^0 ($CHCl_3$). Calculated for $C_{30}H_{48}SO_8$ (568.75): C 63.35%, H 8.51%; Found: C 62.7%, H 8.4%. CI-MS: *m/z* 569 ($M^+ + 1$), 497 ($M^+ - (CH_3)_2CO - CH_2$), 243 ($M^+ - CH_3(CH_2)_{11}C_6H_4SO_2O$), 185 ($M^+ - CH_3(CH_2)_{11}C_6H_4SO_2O - (CH_3)_2CO$). ^{1}H-NMR ($CDCl_3$): δ 7.86, 7.30 (m, 4H, phenyl), 4.64 (d, 1H, $J_{3,4}$ 7.6 Hz, H-3), 4.29-4.00 (m, 6H, H-1ab, H-4, H-5, H-6ab), 1.63 (m, 2H, $OSO_2C_6H_4C\underline{H}_2CH_2(CH_2)_9CH_3$), 1.58 (m, 2H, $OSO_2C_6H_4CH_2C\underline{H}_2(CH_2)_9CH_3$), 1.25 (m, 18H, $OSO_2C_6H_4CH_2CH_2(C\underline{H}_2)_9CH_3$), 1.48, 1.42, 1.33, 1.25 (4s, 12H, CH_3), 0.86 (t, 3H, $ORC\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 155-127 (6x, phenyl), 112.58, 109.52 (qC, acetal), 103.18 (C-2), 78.11, 74.90, 74.01 (C-3, C-4, C-5)[14], 71.61 (C-1), 60.02 (C-6), 48-20 ($OSO_2C_6H_4(\underline{C}H_2)_{11}CH_3$), 27.90, 26.64, 26.12, 25.59 ($\underline{C}H_3$ acetal), 14.02 ($OSO_2Ph(CH_2)_{11}\underline{C}H_3$) ppm.

2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose 1-(p-dodecylbenzenesulphonate) (**11**). A stirred cooled solution of the diacetal **3** (1.50 g, 5.8 mmol) in pyridine (4 ml) was treated with **5** (2.33 g, 6.5 mmol) in the same manner as described above, but for 2 d, followed by column chromatography (hexane/ethyl acetate, 3:1) of the crude product to afford **11** as an orange oil (3.15 g, 96%). $[\alpha]_D$ -54.2^0 ($CHCl_3$). Calculated for $C_{30}H_{48}SO_8$ (568.75): C 63.35%, H 8.51%; Found: C 63.4%, H 8.5%. CI-MS: *m/z* 569 ($M^+ + 1$), 497 ($M^+ - (CH_3)_2CO - CH_2$), 243 ($M^+ - CH_3(CH_2)_{11}C_6H_4SO_2O$), 185 ($M^+ - CH_3(CH_2)_{11}C_6H_4SO_2O - (CH_3)_2CO$). ^{1}H-NMR ($CDCl_3$): δ 7.82, 7.32 (m, 4H, phenyl), 4.56 (dd, 1H, $J_{4,5}$ 7.9 Hz, H-4), 4.28 (d, 1H, $J_{3,4}$ 1.1 Hz, H-3), 4.19 (d, 1H, H1a), 4.09 (d, 1H, H1b), 4.05 (dd, 1H, H-5), 3.86 (d, 1H, $J_{6a,6b}$ 12.9 Hz, H-6a), 3.71 (d, 1H, H-6b), 1.62 (m, 2H, $OSO_2C_6H_4C\underline{H}_2CH_2(CH_2)_9CH_3$), 1.55 (m, 2H, $OSO_2C_6H_4CH_2C\underline{H}_2(CH_2)_9CH_3$), 1.23 (m, 18H, $OSO_2C_6H_4CH_2CH_2(C\underline{H}_2)_9CH_3$), 1.38 (2x), 1.23 (2x) (4s, 12H, CH_3), 0.86 (t, 3H, $ORC\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 155-128 (6x, phenyl), 109.14, 109.03 (qC, acetal), 100.66 (C-2), 70.57, 69.98, 69.68 (C-3, C-4, C-5)[14], 69.14 (C-1), 61.25 (C-6), 48-20 ($OSO_2C_6H_4(\underline{C}H_2)_{11}CH_3$), 26.45, 25.73, 25.10, 23.94 ($\underline{C}H_3$ acetal), 14.04 ($OSO_2Ph(CH_2)_{11}\underline{C}H_3$) ppm.

1,2-O-Isopropylidene-α-D-glucofuranose 3-(1'-decanesulphonate) (**12**). A solution of **6** (517 mg, 1.11 mmol) in 80% aqueous acetic acid (5ml) was stirred at room temperature for 3 days. The

mixture was concentrated *in vacuo*, dissolved in ethyl acetate (50 ml) and the solution washed with 10% aqueous sodium chloride solution (3 x 25 ml), dried (Na_2SO_4), and concentrated *in vacuo* to afford **12** as a colorless oil (372 mg, 79%). $[\alpha]_D$ -0.1^0 ($CHCl_3$). Calculated for $C_{19}H_{36}SO_8$ (424.56): C 53.75%, H 8.55%, S 7.55%; Found: C 53.42%, H 8.39%, S 7.06%. CI-MS: *m/z* 425 ($M^+ + 1$), 409 ($M^+ - CH_3$). ^{1}H-NMR ($CDCl_3$): δ 5.93 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 5.14 (d, 1H, $J_{3,4}$ 2.6 Hz, H-3), 4.74 (d, 1H, H-2), 4.23 (dd, 1H, $J_{4,5}$ 8.8 Hz, H-4), 3.86 (m, 2H, H-5, H-6b), 3.73 (dd, 1H, $J_{6a,6b}$ 12.3 Hz, H-6a), 3.22 (t, 2H, $OSO_2C\underline{H}_2CH_2CH_2(CH_2)_6CH_3$), 1.88 (m, 2H, $OSO_2CH_2C\underline{H}_2CH_2(CH_2)_6CH_3$), 1.45 (m, 2H, $OSO_2CH_2CH_2C\underline{H}_2(CH_2)_6CH_3$), 1.27 (m, 12H, $OSO_2CH_2CH_2CH_2(C\underline{H}_2)_6CH_3$), 1.51, 1.32 (2s, 6H, CH_3), 0.88 (t, 3H, $OSO_2Ph(CH_2)_{11}C\underline{H}_3$) ppm.

In another experiment a stirred solution of **6** (708 mg, 1.52 mmol) in methanol (15 ml) was treated with iodine (75 mg, 0.5% w/v) at room temperature for 2 days. The mixture was then treated with solid sodium thiosulphate until colourless, filtered, and concentrated *in vacuo*. The mixture was dissolved in ethyl acetate (50 ml), washed with 10% aqueous sodium chloride solution (3 x 25 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give **12** as a colorless oil (513 mg, 79%). $[\alpha]_D$ -0.2^0 ($CHCl_3$). The ^{1}H-NMR spectrum of the product was identical to that described above.

5,6-Di-O-acetyl-1,2-O-isopropylidene-α-D-glucofuranose 3-(1'-decanesulphonate) (**13**). Compound **12** (372 mg, 0.88 mmol) was acetylated in the usual manner with acetic anhydride and pyridine. Column chromatography (hexane/ethyl acetate, 4:1) of the crude product afforded **13** as a yellow oil (370 mg, 84%). $[\alpha]_D$ -34.6^0 ($CHCl_3$), GLC-analysis: R_t 16.82 (100%). ^{1}H-NMR ($CDCl_3$, COSY): δ 5.95 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 5.18 (m, 1H, H-5), 5.12 (d, 1H, $J_{3,4}$ 2.6 Hz, H-3), 4.82 (d, 1H, H-2), 4.60 (dd, 1H, $J_{6a,6b}$ 12.4 Hz, H-6a), 4.49 (dd, 1H, $J_{4,5}$ 9.6 Hz, H-4), 4.12 (m, 1H, $J_{6b,5}$ 2.3 Hz, H-6b), 3.14 (m, 2H, $OSO_2C\underline{H}_2CH_2CH_2(CH_2)_6CH_3$), 2.06 (ds, 6H, CH_3 acetyl), 1.83 (m, 2H, $OSO_2CH_2C\underline{H}_2CH_2(CH_2)_6CH_3$), 1.43 (m, 2H, $OSO_2CH_2CH_2C\underline{H}_2(CH_2)_6CH_3$), 1.27 (m, 12H, $OSO_2CH_2CH_2CH_2(C\underline{H}_2)_6CH_3$), 1.52, 1.33 (2s, 6H, CH_3), 0.88 (t, 3H, $ORC\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 170.58, 169.84 (C=O acetyl), 105.09 (qC, acetal), 105.09 (C-1), 82.83, 78.02, 76.34, 67.31 (C-2, C-5, C-3, C-4)[14], 62.97 (C-6), 51.16, 31.78, 29.37, 29.18, 28.80, 28.03, 23.05, 22.59 ($OSO_2(\underline{C}H_2)_9CH_3$), 26.62, 26.23 ($\underline{C}H_3$ acetal), 14.03 ($OSO_2(CH_2)_9\underline{C}H_3$) ppm.

1,2-O-Isopropylidene-β-D-fructopyranose 3-(1'-decanesulphonate) (**14**). A solution of **7** (502 mg, 1.08 mmol) in 80% aqueous acetic acid (5ml) was stirred at room temperature for 7 days. The mixture was concentrated *in vacuo*, dissolved in ethyl acetate (50 ml) and then washed with 10% aqueous sodium chloride solution (3 x 25 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give a solid (434 mg, 94%) which was recrystallized (diisopropyl ether) to afford **14** (202 mg, 44%), m.p. 100-101^{0}C, $[\alpha]_D$ -86.3^0 ($CHCl_3$). Calculated for $C_{19}H_{36}SO_8$ (424.56): C 53.75%, H 8.55%, S 7.55%; Found: C 53.65%, H 8.41%, S 6.81%. CI-MS: *m/z* 425 ($M^+ + 1$), 409 ($M^+ - CH_3$), 185 ($M^+ - RSO_2H - (CH_3)_2CO$). ^{1}H-NMR ($CDCl_3$): δ 4.82 (d, 1H, $J_{3,4}$ 9.4 Hz, H-3), 4.20 (d, 1H, H-4), 4.04 (m, 3H, H-5, H-1ab), 3.99 (d, 1H, $J_{6a,6b}$ 12.6 Hz, H-6a), 3.84 (d, 1H, H-6b), 3.28 (m, 2H, $OSO_2C\underline{H}_2CH_2CH_2(CH_2)_6CH_3$), 1.92 (m, 2H, $OSO_2CH_2C\underline{H}_2CH_2(CH_2)_6CH_3$), 1.43 (m, 2H, $OSO_2CH_2CH_2C\underline{H}_2(CH_2)_6CH_3$), 1.26 (m, 12H, $OSO_2CH_2CH_2CH_2(C\underline{H}_2)_6CH_3$), 1.49, 1.43 (2s, 6H, CH_3), 0.88 (t, 3H, $ORC\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 112.27, (qC, acetal), 103.90 (C-2), 76.55,

69.54, 69.28 (C-3, C-4, C-5)[14], 71.99 (C-1), 63.73 (C-6), 51.45, 31.81, 29.40, 29.21, 28.91, 28.10, 23.35, 22.62 ($OSO_2(\underline{C}H_2)_9CH_3$), 26.17, 26.05 ($\underline{C}H_3$ acetal), 14.60 ($OSO_2(CH_2)_9\underline{C}H_3$) ppm.

In another experiment a stirred solution of **7** (704 mg, 1.52 mmol) in methanol (10 ml) was treated with iodine (100 mg, 1.0% w/v) and set aside at room temperature for 1.5 days. The mixture was then treated with solid sodium thiosulphate until colourless, filtered, and concentrated *in vacuo*. The mixture was dissolved in ethyl acetate (50 ml), washed with 10% aqueous sodium chloride solution (3 x 25 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give a solid (591 mg, 91%) which was recrystallized (diisopropyl ether) to afford **14** (327 mg, 51%), m.p. 100-101^{0}C, $[\alpha]_D$ -84.9^0 ($CHCl_3$). The ^{1}H-NMR and ^{13}C-NMR spectra of the product were identical to those described above.

4,5-Di-O-acetyl-1,2-O-isopropylidene-β-D-fructopyranose 3-(1'-decanesulphonate) (**15**). Compound **14** (199 mg, 0.47 mmol) was acetylated in the usual manner with acetic anhydride and pyridine. Column chromatography (hexane/ethyl acetate, 4:1) of the crude product afforded gave **15** (208 mg, 87%), m.p. 41-42^{0}C. $[\alpha]_D$ -92.9^0 ($CHCl_3$), GLC-analysis: R_t 16.13 (100%). ^{1}H-NMR ($CDCl_3$, COSY): δ 5.37 (d, 1H, $J_{4,5}$ 3.5 Hz, H-4), 5.34 (m, 1H, H-5), 4.97 (d, 1H, $J_{3,4}$ 10.2 Hz, H-3), 4.29 (d, 1H, $J_{1a,1b}$ 9.5 Hz, H-1a), 4.09 (d, 1H, H-6b), 4.04 (d, 1H, H-1b), 3.76 (d, 1H, $J_{6a,6b}$ 13.0 Hz, H-6a), 3.13 (m, 2H, $OSO_2C\underline{H}_2CH_2CH_2(CH_2)_6CH_3$), 2.16, 2.06 (2s, 6H, CH_3 acetyl), 1.88 (m, 2H, $OSO_2CH_2C\underline{H}_2CH_2(CH_2)_6CH_3$), 1.39 (m, 2H, $OSO_2CH_2CH_2C\underline{H}_2(CH_2)_6CH_3$), 1.26 (m, 12H, $OSO_2CH_2CH_2CH_2(C\underline{H}_2)_6CH_3$), 1.49, 1.44 (2s, 6H, CH_3), 0.88 (t, 3H, $OSO_2(CH_2)_9C\underline{H}_3$) ppm.

Reaction of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3-(1'-decanesulphonate) (**6**) *with methanol containing iodine.* A stirred solution of **6** (452 mg, 0.97 mmol) in methanol (10 ml) was treated with iodine (50 mg, 0.5% w/v) and the mixture was heated under reflux for 10 h. The cooled solution was treated with sodium thiosulphate until colourless, filtered and concentrated *in vacuo* to give a colourless syrup. Column chromatography (hexane/ethyl acetate, 1:3) of the crude product afforded a mixture of the methyl D-glucofuranosides **17** and **18** and the methyl D-glucopyranosides **19** and **20** as a syrup (140 mg, 36%). ^{13}C-NMR (IGDE, $CDCl_3$): δ C-1 signals for compounds **17**, **18**, **19** and **20** were detected at 103.86, 112.66, 101.93 and 109.37 ppm, respectively. From the the integration of the C-1 signals in the IGDE ^{13}C-NMR spectrum the ratio of compounds **17**, **18**, **19** and **20** was calculated to be 7:5:25:63.

Reaction of 1,2:4,5-di-O-isopropylidene-β-D-fructopyranose 3-(1'-decanesulphonate) (**7**) *with methanol containing iodine.* A stirred solution of **7** (702 mg, 1.51 mmol) in methanol (10 ml) was treated with iodine (100 mg, 1.0% w/v) and the mixture was heated under reflux for 8 h and then processed as described above. Column chromatography (hexane/ethyl acetate, 1:3) of the crude product afforded pure compound **21** (184 mg, 31%), $[\alpha]_D$ +49.5^0 ($CHCl_3$) as a syrup. ^{1}H-NMR ($CDCl_3$): δ 4.98 (d, 1H, $J_{3,4}$ 5.9 Hz, H-3), 4.41 (t, 1H, $J_{4,5}$ 5.4 Hz, H-4), 3.96 (m, 1H, $J_{5,6a}$ 2.5 Hz, H-5), 3.86 (dd, 1H, $J_{6a,6b}$ 12.3 Hz, H-6a), 3.73 (d, 2H, H-1a, H-6b), 3.61 (d, 1H, $J_{1b,1a}$ 12.3 Hz, H-1b), 3.35 (s, 3H, OCH_3), 3.26 (m, 2H, $OSO_2C\underline{H}_2CH_2CH_2(CH_2)_6CH_3$), 1.86 (m, 2H, $OSO_2CH_2C\underline{H}_2CH_2(CH_2)_6CH_3$), 1.43 (m, 2H, $OSO_2CH_2CH_2C\underline{H}_2(CH_2)_6CH_3$), 1.27 (m, 12H, $OSO_2CH_2CH_2CH_2(C\underline{H}_2)_6CH_3$), 0.88 (t, 3H, $OSO_2(CH_2)_9C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$, DEPT-135): δ 106.25 (C-2), 81.85, 73.58, 86.64 (C-3, C-4, C-5)[14], 60.52 (C-1), 60.69 (C-6), 49.05 (OCH_3),

53.36, 51.13, 31.74, 29.36, 29.17, 28.89, 28.05, 23.15, 22.54 ($OSO_2(\underline{C}H_2)_9CH_3$), 13.96 ($OSO_2(CH_2)_9\underline{C}H_3$) ppm. Further elution gave a mixture of **22** and **23** (170 mg, 28%) as a syrup. ^{13}C-NMR (IGDE, $CDCl_3$): δ C-2 signals for compounds **22** and **23** were detected at 103.51 and 99.88 ppm, respectively. From the the integration of the C-1 signals in the ^{13}C-NMR spectrum the ratio of compounds **22** and **23** was calculated to be 7:3.

Reaction of 2,3:4,5-di-O-isopropylidene-β-D-fructopyranose 1-(1'-decanesulphonate) (**8**) *with methanol containing iodine.* A stirred solution of **8** (508 mg, 1.09 mmol) in methanol (10 ml) was treated with iodine (100 mg, 1.0% w/v) and the mixture was heated under reflux for 14 h and then processed as described above. Column chromatography (hexane/ethyl acetate, 1:3) of the crude product afforded pure compound **24** (162 mg, 37%), $[\alpha]_D$ +57.5^0 ($CHCl_3$) as a syrup. ^{1}H-NMR ($CDCl_3$): δ 4.32 (d, 1H, $J_{1a,1b}$ 11.1 Hz, H-1a), 4.27 (d, 1H, H-1b), 3.98 (m, 3H, H-3, H-4, H-5), 3.76 (dd, 1H, $J_{6a,6b}$ 11.5 Hz, H-6a), 3.69 (d, 2H, H-1a, H-6b), 3.29 (s, 3H, OCH_3), 3.12 (m, 2H, $OSO_2C\underline{H}_2CH_2CH_2(CH_2)_6CH_3$), 1.76 (m, 2H, $OSO_2CH_2C\underline{H}_2CH_2(CH_2)_6CH_3$), 1.36 (m, 2H, $OSO_2CH_2CH_2C\underline{H}_2(CH_2)_6CH_3$), 1.20 (m, 12H, $OSO_2CH_2CH_2CH_2(C\underline{H}_2)_6CH_3$), 0.81 (t, 3H, $OSO_2(CH_2)_9C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$, DEPT-135): δ 107.78 (C-2), 79.06, 78.16, 87.12 (C-3, C-4, C-5)[14], 61.54 (C-1), 62.98 (C-6), 48.94 (OCH_3), 53.00, 50.59, 31.77, 29.39, 29.20, 28.93, 28.07, 23.29, 22.57 ($OSO_2CH_2(\underline{C}H_2)_8CH_3$), 14.01 ($OSO_2(CH_2)_9\underline{C}H_3$) ppm. Further elution gave a mixture of **25** and **26** (168 mg, 39%) as a syrup. ^{13}C-NMR (IGDE, $CDCl_3$): δ C-2 signals for compounds **25** and **26** were detected at 101.18 and 98.87 ppm, respectively. From the the integration of the C-1 signals in the ^{13}C-NMR spectrum the ratio of compounds **22** and **23** was calculated to be 7:3.

3-O-(10'-Bromodec-1'-yl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**27**). A solution of **1** (1.50 g, 5.8 mmol) in DMSO (4 ml) was added dropwise to a stirred mixture of 1,10-dibromodecane (6.95 g, 23.1 mmol) and finely powdered sodium hydroxide (0.69 g, 17.3 mmol) in DMSO (14 ml), and the mixture was then stirred at room temperature for a further 10 h. The mixture was dissolved in dichloromethane (50 ml) and then washed with 10% aqueous sodium chloride solution (3 x 25 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give a syrup. Column chromatography (hexane/ethyl acetate, 8:1) of the crude product afforded compound **27** (2,33 g, 84%) as a colourless syrup. GLC-analysis: R_t 15.08 (**27**, 83%), 10.96 (decene, 6%). ^{1}H-NMR ($CDCl_3$): δ 5.87 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 4.52 (d, 1H, H-2), 4.30 (m, 1H, $J_{5,6a}$ 6.1 Hz, H-5), 4.13 (dd, 1H, $J_{4,5}$ 7.4 Hz, H-4), 4.08 (dd, 1H, $J_{6a,6b}$ 8.5 Hz, H-6a), 3.98 (dd, 1H, H-6b), 3.85 (d, 1H, $J_{3,4}$ 3.0 Hz, H-3), 3.60, 3.51 (2m, 2H, $OC\underline{H}_2(CH_2)_6CH_2CH_2CH_2Br$), 3.41 (t, 1H, $OCH_2(CH_2)_6CH_2CH_2C\underline{H}_2Br$), 1.85 (m, 2H, $OCH_2(CH_2)_6CH_2C\underline{H}_2CH_2Br$), 1.55 (m, 2H, $OCH_2(CH_2)_6C\underline{H}_2CH_2CH_2Br$), 1.28 (m, 12H, $OCH_2(C\underline{H}_2)_6CH_2CH_2CH_2Br$), 1.50, 1.43, 1.39, 1.35 (4s, 12H, CH_3) ppm.

3-O-(10'-Bromodec-1'-yl)-1,2:4,5-di-O-isopropylidene-β-D-fructopyranose (**28**). A solution of **2** (1.50 g, 5.8 mmol) in DMSO (4 ml) was added dropwise to a stirred mixture of 1,10-dibromodecane (5.20 g, 17.3 mmol) and finely powdered sodium hydroxide (0.69 g, 17.3 mmol) in DMSO (14 ml), and then the mixture was stirred at room temperature for a further 11 h and then processed as described above. Column chromatography (hexane/ethyl acetate, 7:1) of the crude

product afforded compound **28** (2,15 g, 71%) as a yellow oil. GLC-analysis: R_t 14.63 (**28**, 90%), 10.80 (decene, 10%). ^{1}H-NMR ($CDCl_3$): δ 4.26 (t, 1H, $J_{4,5}$ 5.7 Hz, H-4), 4.19 (m, 1H, H-5), 4.11 (dd, 1H, $J_{6a,6b}$ 13.4 Hz, H-6a), 4.10 (d, 1H, $J_{1a,1b}$ 8.4 Hz, H-1a), 3.99 (d, 1H, H-6b), 3.94 (d, 1H, H-1b), 3.34 (d, 1H, $J_{3,4}$ 7.3 Hz, H-3), 3.89, 3.47 (2m, 2H, $OC\underline{H}_2(CH_2)_6CH_2CH_2CH_2Br$), 3.40 (t, 1H, $OCH_2(CH_2)_6CH_2CH_2C\underline{H}_2Br$), 1.85 (m, 2H, $OCH_2(CH_2)_6CH_2C\underline{H}_2CH_2Br$), 1.57 (m, 2H, $OCH_2(CH_2)_6C\underline{H}_2CH_2CH_2Br$), 1.29 (m, 12H, $OCH_2(C\underline{H}_2)_6CH_2CH_2CH_2Br$), 1.54, 1.50, 1.40, 1.37 (4s, 12H, CH_3) ppm.

1-O-(10'-Bromodec-1'-yl)-2,3:4,5-di-O-isopropylidene-β-D-fructopyranose (**29**). A solution of **3** (1.51 g, 5.8 mmol) in DMSO (4 ml) was added dropwise to a stirred mixture of 1,10-dibromodecane (6.95 g, 23.1 mmol) and finely powdered sodium hydroxide (0.69 g, 17.3 mmol) in DMSO (14 ml), and the mixture was stirred at room temperature for a further 14 h and then processed as described above. Column chromatography (hexane/ethyl acetate, 8:1) of the crude product afforded compound **29** (2,48 g, 89%) as a yellow oil. GLC-analysis: R_t 14.65 (**29**, 78%), 10.81 (decene, 7%).

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose 3-(10'-dec-1'-ylsulphonic acid), sodium salt (**30**). A stirred solution of **27** (2.01 g, 3.46 mmol) in 96% ethanol (6.25 ml) and water (2.25 ml) was treated with sodium sulphite (0.53 g, 4.2 mmol) and heated under reflux for 17 h, whereon a clear solution was obtained. The cooled mixture was concentrated *in vacuo*. The residue was then suspended in warm dichloromethane (200 ml), filtered to remove solid material, and then concentrated *in vacuo* to a solid. The crude solid material was then washed with diisopropyl ether (3 x 10 ml), and dried *in vacuo* (NaOH) to afford **30** as a white solid (1.10 g, 74%). $[\alpha]_D$ -14.2^0 (water). ^{1}H-NMR (D_2O): δ 5.89 (d, 1H, $J_{1,2}$ 3.1 Hz, H-1), 4.62 (d, 1H, H-2), 4.33 (m, 1H, H-5), 4.15 (t, 1H, H-4), 4.07 (t, 1H, $J_{6a,6b}$ 6.7 Hz, H-6a), 3.92 (t, 1H, H-6b), 3.88 (d, 1H, H-3), 3.63, 3.49 (2m, 2H, $OC\underline{H}_2(CH_2)_6CH_2CH_2CH_2SO_3Na$), 2.83 (t, 1H, $OCH_2(CH_2)_6CH_2CH_2C\underline{H}_2SO_3Na$), 1.72 (m, 2H, $OCH_2(CH_2)_6CH_2C\underline{H}_2CH_2SO_3Na$), 1.55 (m, 2H, $OCH_2(CH_2)_6C\underline{H}_2CH_2CH_2SO_3Na$), 1.31 (m, 12H, $OCH_2(C\underline{H}_2)_6CH_2CH_2CH_2SO_3Na$), 1.48, 1.41, 1.35, 1.31 (4s, 12H, CH_3) ppm. ^{13}C-NMR (D_2O): δ 113.48, 110.35 (qC, acetal), 106.29 (C-1), 83.43, 83.14, 73.72, 82.23 (C-2, C-5, C-3, C-4)[14], 67.83 (C-6), 71.76 ($O\underline{C}H_2(CH_2)_8CH_2SO_3Na$), 52.51, 30.57, 30.37, 30.22, 30.00, 29.68, 27.08, 25.61 ($OCH_2(\underline{C}H_2)_8CH_2SO_3Na$), 27.48, 27.37, 26.93, 26.05 ($\underline{C}H_3$ acetal) ppm.

1,2:4,5-Di-O-isopropylidene-β-D-fructopyranose 3-O-(10'-dec-1'-ylsulphonic acid), sodium salt (**31**). A stirred solution of **28** (0.51 g, 0.95 mmol) in 96% ethanol (6.25 ml) and water (2.25 ml) was treated with sodium sulphite (0.20 g, 1.6 mmol) and heated under reflux for 17 h and then processed as described above to give **31** as a white solid (0.52 g, 97%). $[\alpha]_D$ -60.0^0 (water). ^{1}H-NMR (D_2O): δ 4.24 (m, 2H, H-4, H-5), 4.07 (m, 2H, H-6a, H-1a), 3.94 (m, 2H, H-6b, H-1b), 3.38 (d, 1H, H-3), 3.85, 3.38 (2m, 2H, $OC\underline{H}_2(CH_2)_6CH_2CH_2CH_2SO_3Na$), 2.82 (t, 1H, $OCH_2(CH_2)_6CH_2CH_2C\underline{H}_2SO_3Na$), 1.71 (m, 2H, $OCH_2(CH_2)_6CH_2C\underline{H}_2CH_2SO_3Na$), 1.55 (m, 2H, $OCH_2(CH_2)_6C\underline{H}_2CH_2CH_2SO_3Na$), 1.29 (m, 12H, $OCH_2(C\underline{H}_2)_6CH_2CH_2CH_2SO_3Na$), 1.55, 1.51, 1.37, 1.35 (4s, 12H, CH_3) ppm. ^{13}C-NMR (D_2O): δ 113.76, 110.44 (qC, acetal), 105.76 (C-2), 78.04, 78.46, 75.03 (C-3, C-4, C-5)[14], 72.50 (C-1), 61.03 (C-6), 73.47 ($O\underline{C}H_2(CH_2)_8CH_2SO_3Na$), 52.54,

31.00, 30.53, 30.33, 30.24, 30.05, 29.88, 29.74 ($OCH_2(\underline{C}H_2)_8CH_2SO_3Na$), 28.99, 27.83, 27.09, 26.73 ($\underline{C}H_3$ acetal) ppm.

2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose 1-(10'-dec-1'-ylsulphonic acid), sodium salt (**32**). A stirred solution of **29** (2.01 g, 3.5 mmol) in 96% ethanol (6.25 ml) and water (2.25 ml) was treated with sodium sulphite (0.61 g, 4.8 mmol) and heated under reflux for 17 h and then processed as described above to give **32** as a white solid (1.18 g, 67%). $[\alpha]_D$ -16.7^0 (water). ^{1}H-NMR (D_2O): δ 4.37 (m, 2H, H-3, H-5), 3.92 (d, 1H, H-6a), 3.70 (d, 1H, H-6b), 3.57, 3.49 (2d, 2H, H-1ab), 3.57, 3.49 (2m, 2H, $OC\underline{H}_2(CH_2)_6CH_2CH_2CH_2SO_3Na$), 2.83 (t, 1H, $OCH_2(CH_2)_6CH_2CH_2C\underline{H}_2SO_3Na$), 1.68 (m, 2H, $OCH_2(CH_2)_6CH_2C\underline{H}_2CH_2SO_3Na$), 1.53 (m, 2H, $OCH_2(CH_2)_6C\underline{H}_2CH_2CH_2SO_3Na$), 1.27 (m, 12H, $OCH_2(C\underline{H}_2)_6CH_2CH_2CH_2SO_3Na$), 1.53, 1.44, 1.40, 1.35 (4s, 12H, CH_3) ppm. ^{13}C-NMR (D_2O): δ 110.26, 110.18 (qC, acetal), 103.89 (C-2), 71.94, 71.16, 71.01 (C-3, C-4, C-5)[14], 72.84 (C-1), 61.85 (C-6), 73.11 ($O\underline{C}H_2(CH_2)_8CH_2SO_3Na$), 52.53, 30.58, 30.47, 30.27, 29.76, 27.16, 26.59, ($OCH_2(\underline{C}H_2)_8CH_2SO_3Na$), 27.16, 26.27, 25.65, 24.74 ($\underline{C}H_3$ acetal) ppm.

7.5 References and notes

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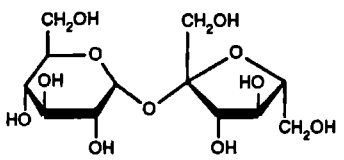
Carbohydrates are a naturally occurring and extremely inexpensive source of chemical raw materials which are available annually from agricultural crops. They are becoming increasingly important as renewable and competitive raw materials for the pharmaceutical and agrochemical industries because of the growing demand for more environmentally friendly processes and products. Carbohydrates as raw materials are attractive since they are stereochemically pure, biodegradable and non-toxic. The great abundance of sucrose (**1**), renders it a potentially attractive and inexpensive starting material for organic synthesis. This thesis deals with the innovative chemical use of sucrose (**1**), its constituent monosaccharides D-glucose (**2**) and D-fructose (**3**) and the oligosaccharide inulin (**4**) for the preparation of potentially useful simple products using alternative and practical methods.



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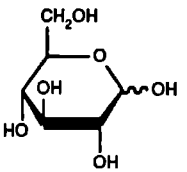

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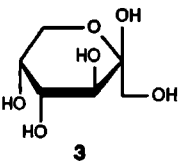

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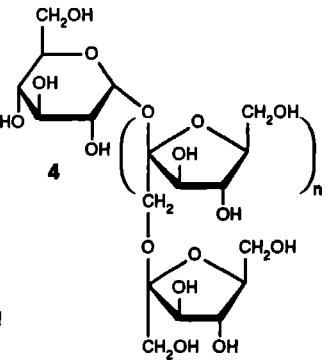

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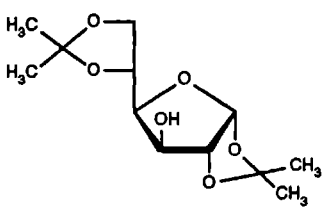
It is well known that selective esterification, and other reactions of sucrose, are difficult to achieve. Esterification of sucrose usually results in the formation of differently substituted esters, and positional isomers thereof, due to the slight differences in reactivity of the eight available hydroxyl groups. In addition, the sensitivity of the glycosidic bond of sucrose towards acid hydrolysis generally necessitates mild reaction conditions.

In Chapter 2 the primary objective was to extend and investigate further the direct selective esterification of sucrose, especially sulphonylation, using sterically hindered sulphonyl chlorides. The synthesis of sucrose sulphonate esters was investigated by direct esterification of **1** using D-(+)-10-camphorsulphonyl chloride, and for comparative reasons, with the long-chain 1-decanesulphonyl chloride. In both cases only mixtures of mono, di- and higher substituted sucrose esters could be isolated and the selective preparation of sulphonate esters was not achieved. The use of partially acetylated sucrose derivatives proved to be more effective for the synthesis of some specific sucrose sulphonate esters. The substrates for these reactions were obtained successfully by an iodine-catalyzed deacetylation process using sucrose octa-acetate in methanol. This reaction led to the formation of a sucrose hepta-acetate and hexa-acetate which were characterized as their corresponding *p*-toluene sulphonate esters.

The synthesis of sucrose phosphates by direct reaction of **1** with the sterically hindered diphenyl phosphorochloridate was investigated. Selective phosphorylation to give higher substituted sucrose derivatives was not achieved, and only mixtures of differently substituted diphenylphosphate esters of sucrose were obtained. More selectivity was obtained in the mono-phosphorylation of sucrose using a controlled amount of this reagent. Detailed ^{1}H, ^{31}P and ^{13}C-NMR analysis of the mono-substituted diphenylphosphate sucrose product revealed that under these conditions phosphorylation, not unexpectedly, occurs preponderantly at the C-6 and C-6' primary positions to an almost equal extent (48 and 41%), followed by the sterically more hindered C-1' position (11%).

Cyclic acetals of sucrose are promising synthetic intermediates, but are difficult to obtain in high yields because of the susceptibility of the interglycosidic bond of sucrose to acid hydrolysis. It is shown that cyclic acetals of sucrose can be prepared, but only in moderate yields, using an newly developed, mild acetalation system of *p*-toluenesulphonic acid in pyridine solution as catalyst.

In Chapter 3 the isopropylidenation of sucrose (**1**), inulin (**4**) and their related monosaccharides D-glucose (**2**) and D-fructose (**3**) is described. A new mild acetalation method using catalytic amounts of iodine in acetone was employed. With sucrose (**1**) very efficient cleavage of the interglycosidic bond occurred, with concomitant isopropylidenation, to yield the di-*O*-isopropylidene acetals **5**, **6** and **7**. The acetals could also be obtained in a direct manner: **5** from D-glucose (**2**), and **6** and **7** from inulin (**4**) or D-fructose (**3**), using the same procedure.



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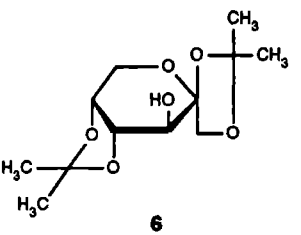

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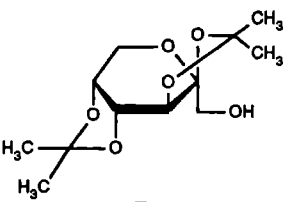
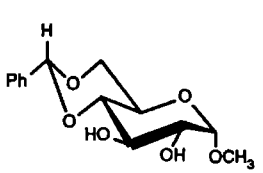


7

There has been considerable interest expressed in the use of **4** as a potential raw material, but only its use in medicine and food technology has been established. Few chemical reactions of **4** have been reported. Regioselectivity would be difficult to control and the sensitivity of the interglycosidic bonds (*cf* sucrose) in the oligosaccharide precludes many reactions. The conventional acid-catalyzed isopropylidenation of **4** is not a convenient source of the acetals **6** and **7**. The iodine-catalyzed isopropylidenation of **4** in boiling acetone afforded the acetal **7** which could be isolated readily by direct crystallization. The reagent combination of iodine in acetone could be used also for the selective cleavage of some common di- and trisaccharides. The disaccharide melibiose could be prepared from the trisaccharide raffinose in this manner. The results obtained using a number of common disaccharides containing only pyranosyl linkages, *i.e.* melibiose, cellobiose, maltose and lactose, indicate that the majority of pyranosyl linkages were unaffected by the acetone-iodine reagent under the standard reaction conditions.

The iodine-catalyzed isopropylidenation could be used also for the synthesis of the di-*O*-isopropylidene acetal **5** directly from D-glucose (**2**), and **6** and **7** directly from D-fructose (**3**). The facile formation of either acetal **7** (82%) or **6** (70%) from D-fructose, by simply performing the reaction in boiling acetone or at room temperature, respectively, is noteworthy.

Further examples of the iodine-catalyzed acetalation reaction using carbonyl reagents other than acetone are described in Chapter 4.



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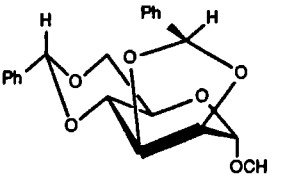

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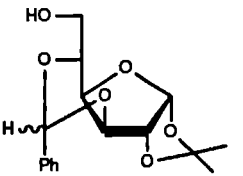
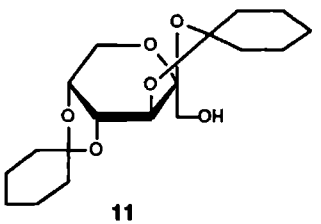


10

It was shown that iodine could be used as a catalyst for the benzylidenation of some model substrates with benzaldehyde dimethylacetal or benzaldehyde as the reagent, but that a suitable solvent must also be employed. This led to an efficient synthesis of methyl 4,6-*O*-benzylidene--α-D-glucopyranoside (**8**), methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside (**9**) and 1,2-*O*-isopropylidene-3,5-*O*-benzylidene-α-D-glucofuranose (**10**).

The iodine-catalyzed acetalation method was used subsequently for the synthesis of the somewhat more unusual cyclohexylidene and cyclopentylidene acetals of D-glucose and D-fructose which are difficultly accessible by the conventional, and less milder methods.



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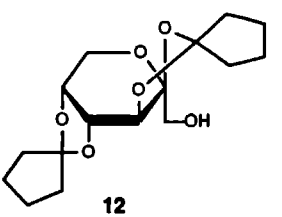
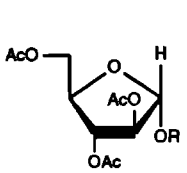


12

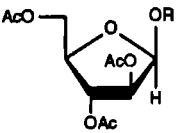
It was possible to obtain the hitherto unknown di-*O*-cyclohexylidene (**11**) and di-*O*-cyclopentylidene (**12**) derivatives of D-fructose under thermodynamically controlled conditions.

It was shown finally that iodine can be used as an efficient catalyst in transacetalation reactions. The di-*O*-isopropylidene acetals of D-glucose (**5**) and D-fructose (**6**) could be selectively transformed into mixed acetals using cyclohexanone in the presence of iodine. Exchange of the isopropylidene acetals takes place, as expected, at the 5,6-position of the D-glucose derivative, and at the 4,5-position of the D-fructose derivative, due to the known differences in stability of the isopropylidene acetal rings in compounds **5** and **6**, respectively.

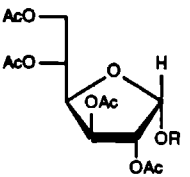
In Chapter 5 a novel and efficient method for the synthesis of a number of short and long-chain alkyl D-fructofuranosides (**13-14**) and D-glucofuranosides (**15-16**) is described, employing a new mild glycosidation method using catalytic amounts of iodine.



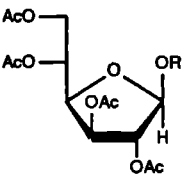
13 R = n-C_nH_{2n+1} n = 1, 2, 3, 4, 8



14 R = n-C_nH_{2n+1} n = 1, 2, 3, 4, 8

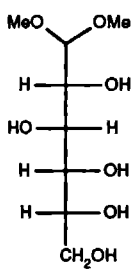


15 R = n-C_nH_{2n+1}, n = 1
17 R = n-C_nH_{2n+1} n = 4, 8, 12



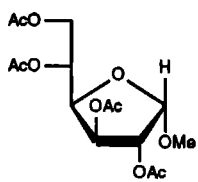
16 R = n-C_nH_{2n+1}, n = 1
18 R = n-C_nH_{2n+1} n = 4, 8, 12

Only a few glycosides of D-fructose (**3**) are known, especially D-fructofuranosides. Iodine was shown to be a very useful alternative catalyst in the direct glycosidation of **3** leading to the formation of D-fructofuranosides (**13-14**) as the main products, which were isolated and characterized as the corresponding peracetates. The procedure is simple and in most cases the pure α-D-fructofuranosides (**13**) could be readily isolated. The scope of the reaction seems to be limited to shorter alcohols, and for longer alcohols an indirect transglycosidation procedure must be employed. It was also possible to use inulin (**4**) in place of D-fructose as the substrate in these reactions. Some of the long-chain alkyl D-fructofuranosides (**13-14**) may be of interest as potential non-ionic surfactants. The iodine-catalyzed glycosidation procedure described could also be used for D-glucose (**2**). D-Glucose exhibited a slightly lower reactivity compared to D-fructose but an efficient synthesis of the methyl D-glucofuranosides (**15-16**) was developed.



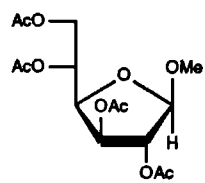
19

1) MeOH / 0.11 equiv I_2
2) Pyr / Ac_2O



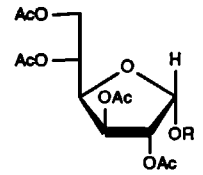
56 %
15

+

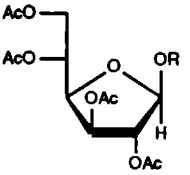


36 %
16

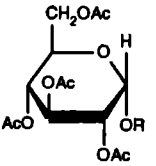
The possible role of D-glucose dimethyl acetal (**19**) in the iodine-catalyzed glycosidation of D-glucose using methanol was investigated. Subjection of **19** to the same reaction conditions of glycosidation for D-glucose in methanol afforded exclusively a mixture of the two methyl D-glucofuranosides **15** and **16** in which the α-furanoside **15** preponderated. This result indicates that the dimethyl acetal is possibly a precursor of the furanosides and not a kinetic product, since the possible formation of pyranosides would then have been expected. Further mechanistic studies will be required to fully clarify these observations.



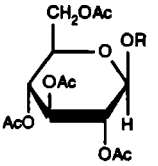
17 R = n-C_nH_{2n+1} n = 4, 8, 12



18 R = n-C_nH_{2n+1} n = 4, 8, 12

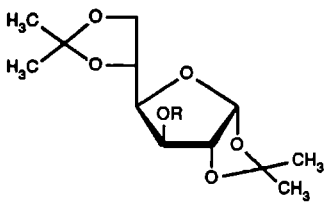


20 R = n-C_nH_{2n+1} n = 4, 8, 12

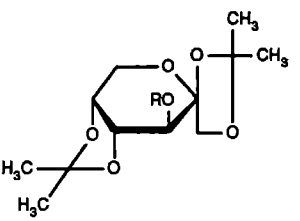


21 R = n-C_nH_{2n+1} n = 4, 8, 12

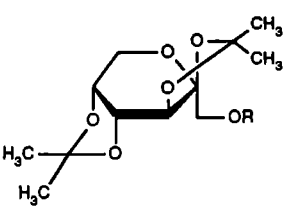
The iodine-catalyzed synthesis of some alkyl D-glucofuranosides (**17-18**) from the readily obtainable 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**5**) is described in Chapter 6. In general, longer reaction times at elevated temperatures were required for the glycosidation of **5** and the desired alkyl D-glucosides were obtained in only moderate yields and characterized as the corresponding peracetates. Despite the use of low catalytic amounts of iodine only mixtures of D-glucosides could be obtained from **5** using the direct or an transglycosidation procedure. The use of more forcing conditions, *i.e.* with higher amounts of iodine (0.5% w/v), led only to the synthesis of the thermodynamically more favoured alkyl D-glucopyranosides (**20-21**).



22 R = $SO_2(CH_2)_9CH_3$
25 R = $SO_2C_6H_4(CH_2)_{11}CH_3$
28 R = $(CH_2)_{10}SO_3Na$



23 R = $SO_2(CH_2)_9CH_3$
26 R = $SO_2C_6H_4(CH_2)_{11}CH_3$
29 R = $(CH_2)_{10}SO_3Na$



24 R = $SO_2(CH_2)_9CH_3$
27 R = $SO_2C_6H_4(CH_2)_{11}CH_3$
30 R = $(CH_2)_{10}SO_3Na$

The synthesis of long-chain alkanesulphonyl esters (**22-27**) and sulphonic acid salts (**28-30**) from the di-*O*-isopropylidene acetals **5**, **6**, and **7** which could be of interest as possible surfactants is described in Chapter 7. Compounds **5**, **6** and **7** were esterified with 1-decanesulphonyl chloride or dodecylbenzenesulphonyl chloride under standard conditions in pyridine to give the corresponding pure alkanesulphonyl esters **22-27** which exhibited some foaming properties when they were brought into contact with water. It is necessary to remove the protecting isopropylidene groups to increase the hydrophilicity of the carbohydrate head-group. The hydrolysis of the 1-decanesulphonyl esters **22-24** was investigated and selective hydrolysis of the esters was found to occur at the expected 5,6-position of compound **22**, and at the 4,5-position of compound **23** when 80% aqueous acetic acid or dilute solutions of iodine in methanol at room temperature were employed. Complete hydrolysis of the esters **22-24** was achieved by the use of dilute solutions of iodine in boiling methanol and led to mixtures of the corresponding methyl D-glycosides.

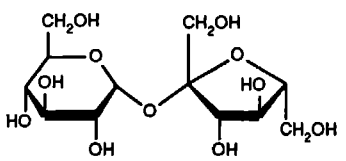
The synthesis of the ionic decyl-ether sulphonates **28-30** from the diacetals **5-7**, as alternatives for the esters **22-27**, was then investigated. The free hydroxyl functions of compounds **5-7** were alkylated using an efficient etherification procedure by treatment with 1,10-dibromodecane in DMSO in the presence of finely powdered sodium hydroxide to give the corresponding bromodecyl ethers. In the second step these alkyl ethers were transformed successfully into the corresponding sulphonate ethers **28**, **29** and **30**, in overall yields of 57%, 69% and 60%, respectively, by treatment with sodium sulphite.

All of the products obtained were stable and exhibited good foaming properties. In order to evaluate the non-ionic esters and ionic ethers as suitable surfactants, the determination of some additional physical properties, such as the critical micelle concentration (CMC) and surface tension, would be required.

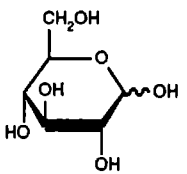
It can be concluded that the reseach, described in this thesis, has led to the development of some new and efficient procedures for the preparation of potentially useful products from sucrose and related compounds. In particular, the use of iodine as catalyst was found to be very useful in acetalation and glycosidation reactions. These reactions could be performed under mild conditions and gave access to some hitherto unknown derivatives. The efficient synthesis of some carbohydrate-based amphiphiles, which may be useful as surfactants, is also described.

Summaries in English and Dutch conclude this thesis.

Koolhydraten vormen een bron van bijzonder goedkope, in de natuur voorkomende, chemische grondstoffen die ieder jaar weer in grote hoeveelheden beschikbaar komen uit landbouwprodukten. Ze worden in toenemende mate belangrijk voor de farmaceutische en agrochemische industrie als hernieuwbare en concurrerende grondstoffen vanwege de groeiende behoefte naar meer milieuvriendelijke processen en produkten. Koolhydraten zijn aantrekkelijk als grondstof, omdat ze stereochemisch zuiver, biologisch afbreekbaar en niet giftig zijn. Sucrose (**1**) is mede door haar overvloedig voorkomen een potentieel zeer aantrekkelijke en goedkope uitgangsstof voor de organische synthese. Dit proefschrift beschrijft het innovative chemische gebruik van sucrose (**1**), zijn monosacchariden D-glucose (**2**) en D-fructose (**3**) en de oligosaccharide inuline (**4**) voor de bereiding van potentieel bruikbare en simpele produkten met gebruik van alternatieve en praktische methoden.



1



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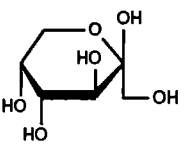

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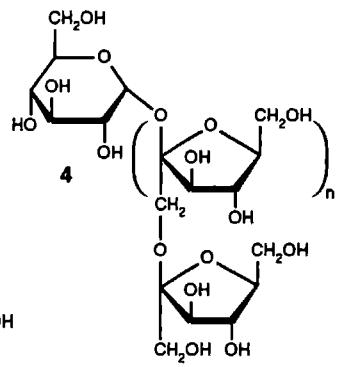


4

Het is bekend dat de selectieve verestering, en andere reacties van sucrose, moeilijk uitvoerbaar zijn. De verestering van sucrose resulteert meestal in de vorming van mengsels van produkten, die verschillen in substitutiegraad en de positie van de substituent ten gevolge van de geringe verschillen in reactiviteit van de acht beschikbare hydroxyl-groepen. Bovendien zijn in het algemeen milde reactie omstandigheden noodzakelijk in verband met de gevoeligheid van de glycosidische binding van sucrose voor zure hydrolyse.

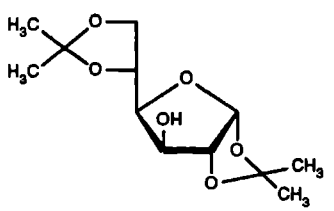
De primaire doelstelling in hoofdstuk 2 is het uitbreiden en verder onderzoeken van de direkte verestering van sucrose, in het bijzonder de sulfonylering, gebruik makend van sterisch gehinderde sulfonylchlorides. De synthese van sucrose-sulfonaatesters werd onderzocht door middel van de direkte verestering van **1** met D-(+)-10-kamfersulfonylchloride, en ter vergelijking, met het lange-keten 1-decaansulfonylchloride. In beide gevallen werden alleen mengsels van mono, di- en hoger gesubstituteerde sucrose-esters geïsoleerd en kon de synthese van specifieke sulfonaatesters niet gerealiseerd worden. Het gebruik van partieel geacetyleerde sucroses bleek beter geschikt te zijn voor de synthese van enige specifieke sucrose-sulfonaatesters. De substraten voor deze reacties

konden goed verkregen worden door gebruik te maken van een jodium-gekatalyseerde deacetyleringsprocedure van sucrose-octa-acetaat in methanol. Met deze reactie kon een specifiek sucrose-hepta-acetaat en -hexa-acetaat verkregen worden die gekarakteriseerd werden als de corresponderende *p*-tolueensulfonaatesters.

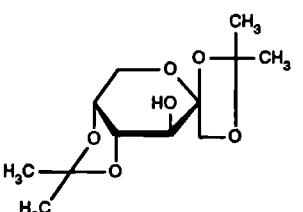
De synthese van sucrosefosfaten werd onderzocht door middel van direkte reactie van **1** met het sterisch gehinderde difenylfosforochloridaat. Selectieve fosforylering tot hoger gesubstiteerde sucrosederivaten kon niet worden gerealiseerd, alleen mengsels van verschillend gesubstitueerde difenylfosfaatesters van sucrose werden verkregen. De mono-fosforylering met behulp van dit reagens verliep daarintegen wel met een hogere selectiviteit. Gedetailleerde ^{1}H-, ^{31}P- en ^{13}C-NMR-analyse van het verkregen sucrose-monodifenylfosfaat toonde aan dat de fosforylering onder deze condities, zoals verwacht, voornamelijk plaats vindt op de primaire C-6 en C-6' posities in gelijke mate (48 en 41%), gevolgd door de meer gehinderde C-1' positie (11%).

Cyclische acetalen van sucrose zijn waardevolle synthetische intermediairen, maar zijn moeilijk in hoge opbrengsten te verkrijgen vanwege de gevoeligheid van de interglycosidische band van sucrose voor zure hydrolyse. Er werd gevonden dat deze cyclische acetalen bereid kunnen worden, zij het in matige opbrengsten, door een nieuw ontwikkeld mild acetaleringssysteem bestaande uit een oplossing van *p*-tolueensulfonzuur in pyridine als katalysator.

In hoofdstuk 3 wordt de isopropylidenering van sucrose (**1**), inuline (**4**) en de verwante monosacchariden D-glucose (**2**) en D-fructose (**3**) beschreven. Daarbij werd gebruik gemaakt van een nieuw ontwikkeld mild acetalerings systeem bestaande uit katalytische hoeveelheden jodium in aceton. Sucrose (**1**) werd zeer efficiënt gesplitst bij de interglycosidische binding, en door tegelijkertijd optredende isopropylidenering werden de di-*O*-isopropylideenacetalen **5**, **6** en **7** verkregen. Deze acetalen konden ook op een direkte manier gesynthetiseerd worden: **5** vanuit D-glucose (**2**), en **6** en **7** vanuit inuline (**4**) of D-fructose (**3**), gebruik makend van dezelfde procedure.



5



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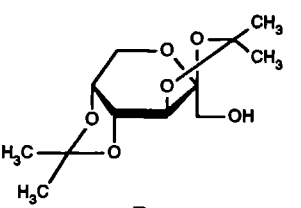


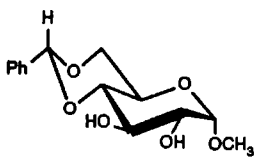
7

Er is een toenemende belangstelling voor het gebruik van inuline (**4**) als een hernieuwbare grondstof. Tot nu toe is alleen het gebruik van **4** in de medicijn- en voedseltechnologie bekend en slechts weinig chemische omzettingen. De regioselectiviteit is moeilijk te controleren en de gevoeligheid van de interglycosidische bindingen (*cf* sucrose) in het oligosaccharide sluit vele reagentia uit. De conventionele zuur-gekatalyseerde isopropylidenering van **4** is niet geschikt voor de synthese van de acetalen **6** en **7**. De jodium-gekatalyseerde isopropylidenering van **4** in

refluxende aceton gaf wel toegang tot het acetaal **7** dat geïsoleerd kon worden door direkte kristallisatie. Het reagens van jodium in aceton kon ook worden gebruikt voor de selectieve splitsing van enige di- en trisacchariden. Op deze manier werd het disaccharide melibiose verkregen uit het trisaccharide raffinose. De behaalde resultaten met een aantal disacchariden die alleen pyranosyl gekoppelde monosacchariden bevatten, *i.e.* melibiose, cellobiose, maltose en lactose, laten zien dat de meerderheid van deze pyranosyl gekoppelde verbindingen niet aangetast worden door het mengsel van jodium in aceton onder de gebruikte reactiecondities.

De jodium-gekatalyseerde isopropylidenering kan ook worden gebruikt voor de synthese van het di-*O*-isopropylideenacetaal **5** direkt vanuit D-glucose (**2**) alsmede de acetalen **6** en **7** direkt vanuit D-fructose (**3**). Vermeldenswaardig is hierbij de gemakkelijke vorming van één van beide acetalen **7** (82%) of **6** (70%) uit D-fructose, door de reactie simpelweg uit te voeren in aceton bij refluxtemperatuur of in aceton bij kamertemperatuur.

In hoofdstuk 4 worden verdere voorbeelden beschreven van de jodium-gekatalyseerde acetaleringsreactie met andere carbonylreagentia dan aceton.



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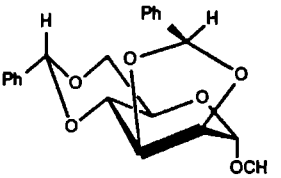
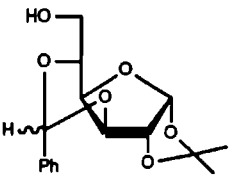


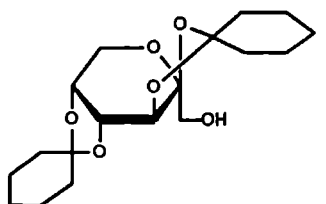
9



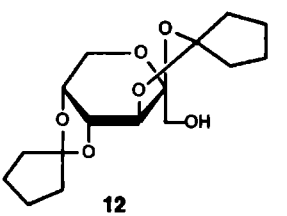
10

Het bleek dat jodium ook gebruikt kan worden als katalysator voor de benzylidenering van enkele modelsubstraten met benzaldehyde of benzaldehyde dimethylacetaal als reagens, mits ook een geschikt oplosmiddel wordt gebruikt. Dit resulteerde in de efficiënte synthese van methyl 4,6-*O*-benzylideen-α-D-glucopyranoside (**8**), methyl 2,3:4,6-di-*O*-benzylideen-α-D-mannopyranoside (**9**) en 1,2-*O*-isopropylideen-3,5-*O*-benzylideen-α-D-glucofuranose (**10**).

De jodium-gekatalyseerde acetaleringsmethode werd vervolgens toegepast voor de synthese van de minder gebruikelijke cyclohexylideen- en cyclopentylideen-acetalen van D-glucose en D-fructose die moeilijk toegankelijk zijn met de conventionele methoden.



11

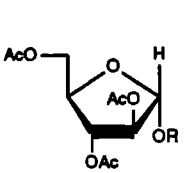


12

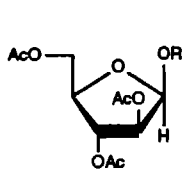
Het was mogelijk om in thermodynamisch gecontroleerde reacties de tot nu toe onbekende di-*O*-cyclohexylideen (**11**) en di-*O*-cyclopentylideen (**12**) derivaten van D-fructose te synthetiseren.

Tot slot werd aangetoond dat jodium gebruikt kan worden als een efficiënte katalysator in trans-acetaleringsreacties. De di-*O*-isopropylideenacetalen van D-glucose (**5**) en D-fructose (**6**) konden selectief omgezet worden in gemengde acetalen door gebruik te maken van cyclohexanon in aanwezigheid van jodium. De substitutie van de isopropylideen acetalen vindt, zoals verwacht, plaats op de 5,6-positie van het D-glucose-derivaat, en op de 4,5-positie van het D-fructose-derivaat, als gevolg van de bekende verschillen in stabiliteit van de isopropylideengroepen in **5** en **6**.

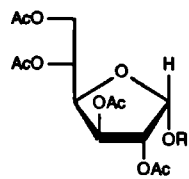
In hoofdstuk 5 wordt een nieuwe en efficiënte methode voor de synthese van een aantal korte- en lange-keten alkyl D-fructofuranosiden (**13-14**) en D-glucofuranosiden (**15-16**) beschreven, gebruik makend van een nieuwe milde glycosideringsmethode met jodium als katalysator.



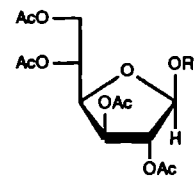
13 R = n-C_nH_{2n+1}
n = 1, 2, 3, 4, 8



14 R = n-C_nH_{2n+1}
n = 1, 2, 3, 4, 8

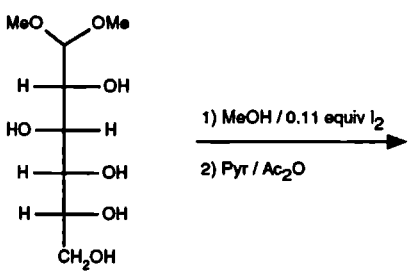


15 R = n-C_nH_{2n+1}, n = 1
17 R = n-C_nH_{2n+1}
n = 4, 8, 12

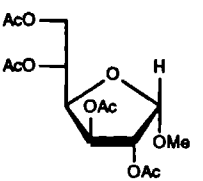


16 R = n-C_nH_{2n+1}, n = 1
18 R = n-C_nH_{2n+1}
n = 4, 8, 12

Slechts enkele glycosiden van D-fructose (**3**) zijn bekend, in het bijzonder D-fructofuranosiden. Jodium bleek een zeer geschikte alternatieve katalysator te zijn voor de direkte glycosidering van **3** en dit resulteerde in de vorming van D-fructofuranosiden (**13-14**) als de hoofdprodukten, die geïsoleerd en gekarakteriseerd werden als de corresponderende peracetaten. De procedure is simpel en in de meeste gevallen konden de zuivere α-D-fructofuranosiden (**13**) gemakkelijk worden geïsoleerd. De scope van de reactie lijkt beperkt tot kortere alcoholen, maar voor langere alcoholen kan een indirekte trans-glycosiderings procedure gebruikt worden. Het was ook mogelijk om inuline (**4**) in plaats van D-fructose te gebruiken als substraat voor deze reacties. Sommige van de lange-keten alkyl D-fructofuranosiden (**13-14**) zijn wellicht interessant als niet-ionogene surfactants. De jodium-gekatalyseerde glycosideringsprocedure kon ook gebruikt worden voor D-glucose (**2**), dat een geringere reactiviteit vertoonde dan D-fructose. Niettemin kon een efficiënte synthese van de methyl D-glucofuranosiden (**15-16**) worden ontwikkeld.



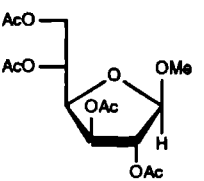
19



56 %

15

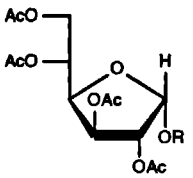
+



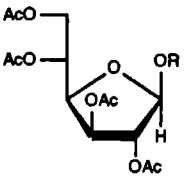
36 %

16

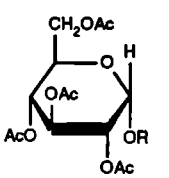
De mogelijke rol van D-glucose-dimethylacetaal (**19**) in de jodium-gekatalyseerde glycosideringsreactie van D-glucose in methanol is onderzocht. Na blootstelling van **19** aan dezelfde reactiecondities als voor de glycosidering van D-glucose, werd een mengsel verkregen van de twee methyl D-glucofuranosiden **15** en **16** waarin het α-furanoside **15** overheerste. Dit resultaat geeft aan dat het dimethylacetaal mogelijk een precursor is van de furanosiden en niet een kinetisch produkt, omdat in dat geval ook de vorming van pyranosiden verwacht kan worden. Verdere mechanistische studies zijn nodig om deze waarnemingen volledig te verklaren.



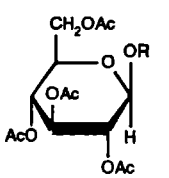
17 R = n-C_nH_{2n+1} n = 4, 8, 12



18 R = n-C_nH_{2n+1} n = 4, 8, 12

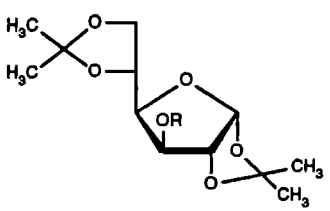


20 R = n-C_nH_{2n+1} n = 4, 8, 12

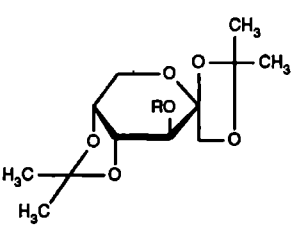


21 R = n-C_nH_{2n+1} n = 4, 8, 12

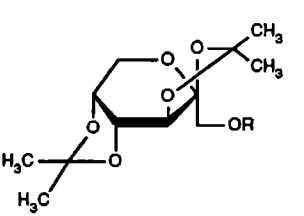
De jodium-gekatalyseerde synthese van enkele alkyl D-glucofuranosiden (**17-18**) is beschreven in hoofdstuk 6, uitgaande van het goed toegankelijke 1,2:5,6-di-*O*-isopropylideen--α-D-glucofuranose (**5**). In het algemeen waren langere reactie tijden bij hogere temperaturen noodzakelijk voor de glycosidering van **5**. De gewenste alkyl D-glucosiden werden verkregen in matige opbrengsten en gekarakteriseerd als de corresponderende peracetaten. Ondanks het gebruik van katalytische hoeveelheden jodium konden vanuit **5** alleen mengsels van D-glucosiden worden verkregen, zowel via de direkte als via een trans-glycosideringsprocedure. Het gebruik van meer geforceerde condities, *i.e.* met hogere jodiumconcentraties (0.5% w/v), resulteerde in de vorming van de alkyl D-glucopyranosiden (**20-21**) als gevolg van de thermodynamisch gecontroleerde reactieomstandigheden.



22 R = $SO_2(CH_2)_9CH_3$
25 R = $SO_2C_6H_4(CH_2)_{11}CH_3$
28 R = $(CH_2)_{10}SO_3Na$



23 R = $SO_2(CH_2)_9CH_3$
26 R = $SO_2C_6H_4(CH_2)_{11}CH_3$
29 R = $(CH_2)_{10}SO_3Na$



24 R = $SO_2(CH_2)_9CH_3$
27 R = $SO_2C_6H_4(CH_2)_{11}CH_3$
30 R = $(CH_2)_{10}SO_3Na$

De synthese van lange-keten alkaansulfonylesters (**22-27**) en sulfonzure natriumzouten (**28-30**) van de di-*O*-isopropylideen acetalen **5**, **6**, en **7**, die mogelijk interessant zijn als surfactants, is beschreven in hoofdstuk 7. Verestering van de verbindingen **5**, **6** en **7** met 1-decaansulfonylchloride of dodecylbenzeensulfonylchloride onder standaardcondities in pyridine gaf de

corresponderende zuivere alkaansulfonylesters **22-27**. Deze esters vertoonden enige schuimvorming wanneer ze in contact werden gebracht met water. Om de hydrofiliciteit van de koolhydraat-kopgroep te vergroten is het noodzakelijk om de beschermende isopropylideengroepen te verwijderen. De hydrolyse van de 1-decaansulfonylesters **22-24** is onderzocht. De selectieve hydrolyse van de acetaalgroep was mogelijk op de verwachte 5,6-positie van verbinding **22** en op de 4,5-positie van verbinding **23**. Hiervoor kon 80% waterige azijnzuur of oplossingen van jodium in methanol bij kamertemperatuur worden gebruikt. Volledige hydrolyse van de acetaalgroepen in **22-24** werd bereikt met gebruik van oplossingen van jodium in methanol bij refluxtemperatuur en daarbij werden mengsels van de corresponderende methyl D-glycosiden gevormd.

De synthese van de ionogene decylethersulfonaten **28-30** uit de diacetalen **5-7**, als alternatief voor de esters **22-27**, is vervolgens onderzocht. De vrije hydroxyl functies van verbindingen **5-7** werden gealkyleerd met 1,10-dibroomdecaan, gebruik makend van een efficiënte veretherings-procedure in DMSO in aanwezigheid van fijn gepoederd natriumhydroxide, en gaf de corresponderende broomdecyl ethers. In de tweede stap konden deze alkyl ethers met success omgezet worden in de corresponderende ethersulfonaten **28**, **29** en **30** door behandeling met natriumsulfiet in totaalopbrengsten van respectievelijk 57%, 69% en 60%.

Alle verkregen produkten waren stabiel en vertoonden goede schuimvormende eigenschappen in water. Om te kunnen beoordelen of de niet-ionogene esters en de ionogene ethers geschikte surfactants zijn is de bepaling van enkele additionele fysische eigenschappen, zoals de critische micelconcentratie (CMC) en oppervlaktespanning noodzakelijk.

Er kan worden geconcludeerd dat het onderzoek, dat is beschreven in dit proefschrift, heeft geleid tot de ontwikkeling van enige nieuwe en efficiënte procedures voor de bereiding van mogelijk nuttige produkten van sucrose en gerelateerde verbindingen. In het bijzonder werd gevonden dat jodium gebruikt kan worden als een zeer geschikte alternatieve katalysator in acetalerings- en glycosideringsreacties. Deze reacties konden worden uitgevoerd onder milde condities en gaven toegang tot de synthese van enkele nieuwe verbindingen. Daarnaast is een efficiënte synthese beschreven van enkele op koolhydraten gebaseerde amfifielen die mogelijk bruikbaar zijn als surfactants.

Samenvattingen in het Engels en Nederlands besluiten dit proefschrift.

CURRICULUM VITAE

Cor Verhart werd op 2 oktober 1964 geboren te Elst. Hij bezocht het Nederrijn College te Arnhem en behaalde er in 1983 het diploma Atheneum-B. In september van datzelfde jaar werd begonnen aan de studie Scheikunde aan de Katholieke Universiteit Nijmegen. In maart 1989 werd het Doctoraal Examen afgelegd met als hoofdvak Organische Chemie (Prof. Dr. G.I. Tesser) en als bijvak Biochemie (Prof. Dr. J. de Pont).
Vanaf mei 1989 tot mei 1993 was hij werkzaam als assistent in opleiding (A.I.O.) aan het laboratorium voor Organische Chemie van de Katholieke Universiteit Nijmegen. In deze periode werd het in dit proefschrift beschreven onderzoek verricht in het kader van een IOP-k projekt onder leiding van Prof. Dr. B. Zwanenburg en Dr. G.J.F. Chittenden.
Gedurende de promotieperiode is hij als practicum assistent betrokken geweest bij het onderwijs aan biologiestudenten.

PUBLICATIONS

- *New base-labile amino-protective groups for peptide synthesis.*
  C.G.J. Verhart and G.I. Tesser.
  Recl. Trav. Chim. Pays-Bas **107**, 621-626 (1988).

- *Acetalation Studies. Part IX. Reaction of sucrose and some related sugars with acetone in the presence of iodine; a novel cleavage-isopropylidenation method.*
  C.G.J. Verhart, B.M.G. Caris, B. Zwanenburg and G.J.F. Chittenden.
  Recl. Trav. Chim. Pays-Bas **111**, 348-352 (1992).

- *Some aspects of the iodine-catalyzed synthesis of cyclohexylidene and cyclopentylidene acetals of D-glucose and D-fructose.*
  C.G.J. Verhart, G.A.P. van Helvoirt, B. Zwanenburg and G.J.F. Chittenden, *in preparation.*

- *Glycosidation of D-glucose, D-fructose and some related compounds catalyzed by iodine.*
  C.G.J. Verhart, C.T.M. Fransen, B. Zwanenburg and G.J.F. Chittenden, *in preparation.*

- *Synthesis of some potential surfactants derived from D-glucose and D-fructose.*
  C.G.J. Verhart, G.A.P. van Helvoirt, B. Zwanenburg and G.J.F. Chittenden, *in preparation.*